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The Journal of Allergy

VOL. 16 NOVEMBER, 1945 No. 6

American Academy of Allergy

First Annual Meeting, New York, N. Y., Dec. 11 and 12, 1944

(Continued)

MEASUREMENT OF CIRCULATING RAGWEED ANTIGEN*†‡

MARY C. JOHNSON, A.B., H. L. ALEXANDER, M.D., J. H. ALEXANDER, A.B., AND H. M. WALKER, M.S., ST. LOUIS, MO.

THIS study was undertaken to investigate the presence of ragweed antigen in the sera of hay fever patients and normal individuals during the ragweed pollen season. In the title of this paper, the word "antigen" is really a misnomer, since ragweed contains many antigens; but for the sake of convenience, the word is employed.

Colonnell,[1] in 1943, reported the presence of ragweed antigen in transfusion sera by testing with such sera sites which had been passively sensitized with reagin to ragweed pollen. Levine and Coca,[2] in 1926, utilized the passive transfer test to detect pollen antigen in the serum and urine of normal subjects who had received large amounts of specific pollen by injection. Brunner and Walzer,[3] Cohen and his co-workers,[4, 5] Feinberg and Bernstein,[6] Walzer and Walzer,[7-9] and others, have used various modifications of the passive transfer test, wherein the appearance of a wheal at a sensitized site, following inhalation, ingestion, or injection of antigen, was used to demonstrate circulating antigen. Precipitin tests for detecting antigens other than pollen in human sera have been employed by Alexander, Shirley, and Allen,[10] Longcope and Rackemann,[11] Tuft,[12] and several other investigators.

Pollen antiserum of high precipitin titer was formerly considered difficult to produce. Recently, however, a method has been devised in this laboratory in which antipollen precipitins have been produced in relatively high titers. Hampton and his co-workers[13] used such antiragweed rabbit serum in measuring the thermostable antibody in the sera of hay fever patients who had received specific treatment.

In this study, the presence of ragweed pollen antigen was demonstrated by the precipitin test, wherein human serum and antiragweed rabbit serum were used under standard experimental conditions. The amount of antigen present was roughly quantitated in terms of precipitate. Although it is

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†Presented, in part, before the First Annual Meeting of the American Academy of Allergy, New York City, Dec. 12, 1944.

‡This investigation was supported by a grant from the John and Mary R. Markle Foundation.

realized that, actually, the precipitate consists mainly of antibody, it was found that, in series, comparative amounts of antigen could be roughly measured by this method.

METHOD

Rabbits were sensitized to ragweed pollen by multiple intramuscular injections of extract adsorbed on aluminum hydroxide gel, according to the method of Hektoen and Welker,[14] with additional subcutaneous injections of staphylococcus toxin. The precipitin titer of each serum was determined, and those having the highest titers were pooled, then frozen and stored at –72° C.

The rabbit serum was diluted 1:4 with physiologic saline solution, a value at which no nonspecific precipitation was observed to appear. This dilution of predetermined precipitin activity was freshly prepared for each day's experiment from the same lot of pooled frozen antiragweed rabbit serum.

Sediment-free human serum was used undiluted usually within twenty-four hours, and never later than forty-eight hours after the blood sample had been drawn, although no studies of deterioration of antigen in serum have as yet been made.

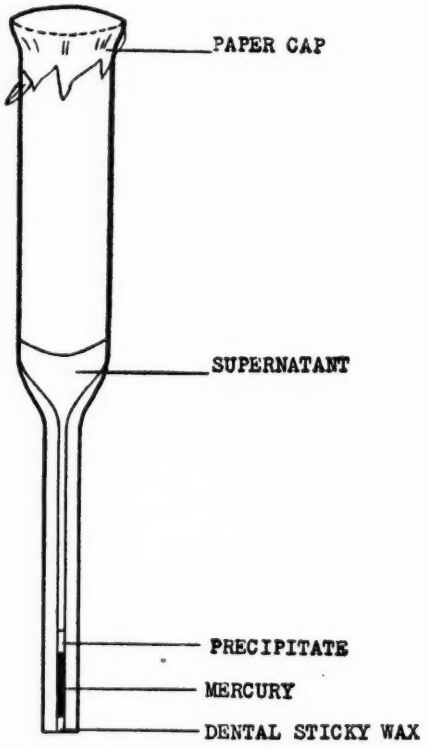

Fig. 1.—Meloche tube.

Precipitation experiments were performed by using special tubes previously described by Johnson, Alexander, Robinson, and Alexander,[15] with a few modifications in technique. Equal volumes (0.25 c.c.) of human and antiragweed rabbit sera were measured directly into chemically clean Meloche tubes (Fig. 1) with an average bore (predetermined for each tube) of about 0.4 mm. after mercury had been drawn into the capillary for a distance of about 1 cm., and the tip sealed with dental sticky wax. It was noted that, when precipitation experiments were performed during the hot summer weather (when the temperature exceeded 36° C.), some evaporation of serum occurred,

and a milky sediment was formed. Consequently, all volumetric measurements were made while the tubes were standing in a water bath at 10° C.

After covering the bowls containing the antigen-antibody mixture with paper caps, the tubes were placed in an automatic shaker for two minutes, incubated at 37° C. in a water bath for one hour, and placed in a refrigerator for about eighteen hours. Then the tubes were gently shaken and placed in centrifuge cups, with the stems inserted into thick rubber tubing to prevent tilting during centrifugation. Centrifugation was performed at 2,500 revolutions per minute for fifteen minutes, a predetermined optimum rate and time.

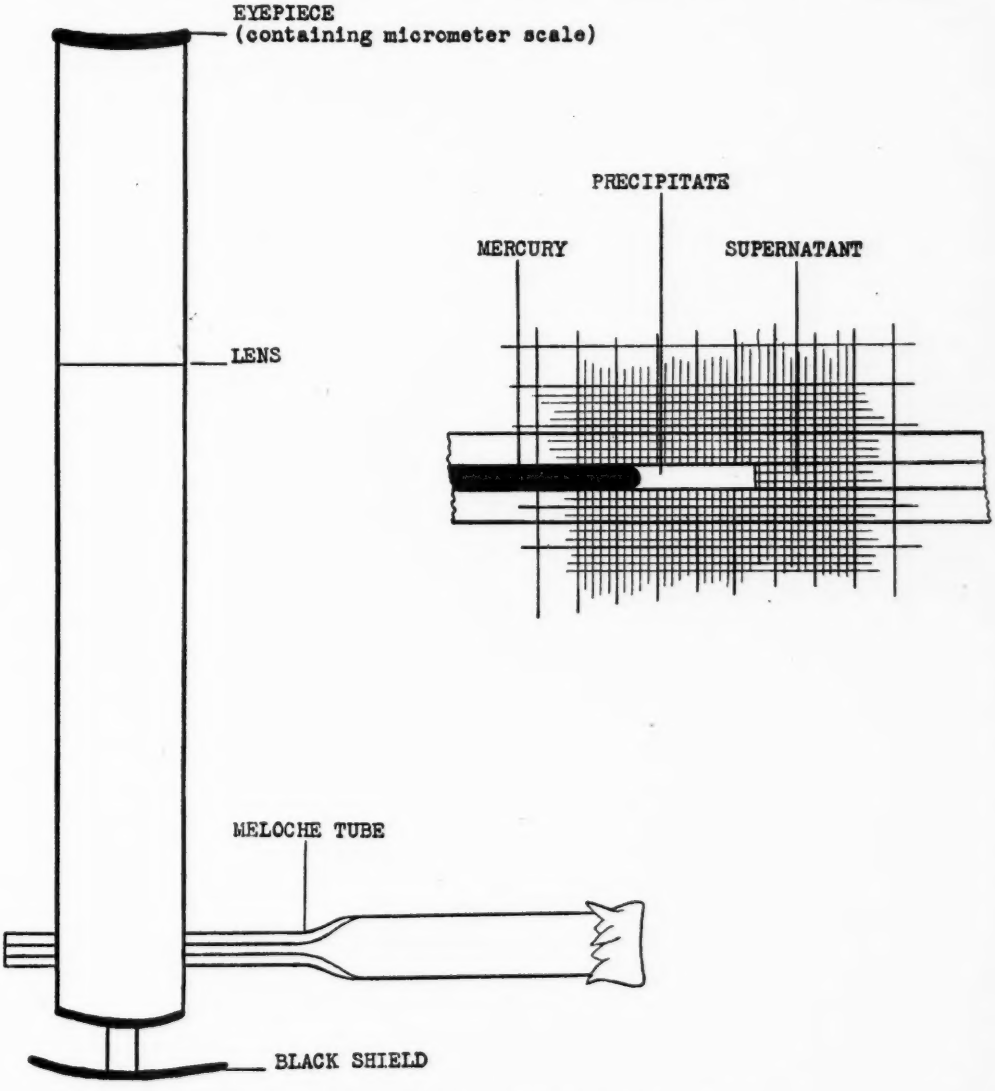

Fig. 2.—Lens system for the Meloche tube.

The length of the packed precipitate in the capillary was measured in a simple optical apparatus (Fig. 2). This consists of a brass tube 20 cm. in length and 2.5 cm. in diameter. The specification of the eye cap is +7 diopters and of the adjacent eyepiece +100 diopters. A lower lens, which is at a distance of 11 cm., has a power of −7 diopters. The magnification of the lens system is, therefore, ×10. A micrometer scale which is calibrated against a known scale is attached to the upper eyepiece. In the apparatus in use, 1 mm. at the

point of focus is equivalent to 25 micrometer scale units. At the far end of the brass tube is a slot in which the stem of the Meloche tube is placed so that the column of precipitate is at the point of focus of the optical field. A black shield is affixed to the brass tube just beyond the slot so that a space of 2 cm. appears between the tube and the shield. A 60-watt light, placed at right angles to the end of the tube, at a distance of about 2 feet, is directed toward the space. This reveals the column of precipitate as white against a comparatively dark background. Since the magnification of the lens system and the bore of each capillary are known, the volume can be calculated from reading the length of the precipitate in terms of micrometer units.*

CONTROLS

All human sera tested for ragweed antigen were mixed separately with antitimothy rabbit serum and with normal rabbit serum. A very few showed precipitation, and these sera were discarded from the study.

Sera which had been obtained during the height of the timothy pollen season and which produced a precipitate when mixed with antitimothy rabbit serum failed to produce a precipitate when mixed with antiragweed rabbit serum.

All sera of ragweed sensitive patients obtained previous to the ragweed pollen season also failed to produce precipitation with antiragweed rabbit serum.

Likewise, preseasonal sera from normal, nonsensitive individuals failed to produce a precipitate with antiragweed rabbit serum. However, coseasonal and postseasonal specimens from the same individuals conformed to the variations that occurred in the sera of patients with ragweed hay fever.

Precipitation produced by sera obtained after the pollen season, diminished in quantity and finally disappeared.

OBSERVATIONS

Of 311 sera obtained at frequent intervals throughout the 1944 ragweed pollen season, 207 (66 per cent) showed precipitation.

Inasmuch as the essential purpose of this study was to measure and demonstrate circulating ragweed antigen, samples were secured from various sources, as from patients in the outpatient department, among laboratory personnel, and from private practice. Accurate, comparative data on clinical results and treatment were, therefore, not obtained. However, a broad correlation between the amount of antigen, as measured in terms of precipitate, and of the patient's clinical symptoms at the time the blood was drawn was made. The symptoms were classified into two groups: (A) moderate and severe, and (B) none or mild.

One hundred forty-six sera were from patients in Group A, 148 were from patients in Group B, and there were 17 sera from normal individuals.

Precipitation data are summarized in Table I. It is interesting to note from the percentage of sera showing precipitation and the average volume of precipitate for each group, that, as a group, patients with few symptoms showed comparatively less precipitate.

The reflection of the amount of ragweed pollen extract injected on the amount recovered in the blood is being studied. Levine and Coca[2] reported that timothy antigen injected intravenously into normal individuals in large

*Calculation: Length of column of precipitate (in micrometer units) ------ = A
½ diameter of capillary, squared, × 3.1416 (πR^2) ---------- = B
Magnification of lens system ---------- = C

$$\frac{A \times B}{C} = \text{volume of precipitate in cubic millimeters.}$$

Experimental error = ± 0.001 cu. mm.

TABLE I. PRECIPITATION IN SEASONAL SERA OF RAGWEED HAY FEVER PATIENTS

GROUP (SYMPTOMS)	NUMBER OF SERA	NUMBER SHOWING PRECIPITATION	PERCENTAGE SHOWING PRECIPITATION	AVERAGE VOLUME OF PRECIPITATE PER 0.25 C.C. OF SERUM IN CU. MM.
A. Moderate and severe	146	118	81	0.048
B. None or mild	148	83	56	0.025
Normal	17	6	35	0.019

doses remained in the circulation for as long as seven days after injection. However, in pollen sensitive patients who had received specific treatment over a protracted period of time, they found that no injected pollen antigen was retained in the blood, as detected by passive transfer tests. Langner and Kern[16] found that pollen extract injected subcutaneously was eliminated within forty-eight hours.

In this study, it is presumed that the injected antigen may not be of much significance in increasing the amount of circulating antigen since untreated patients, by and large, showed most precipitate. Moreover, in no instance was precipitate found in sera obtained previous to the pollen season, even when patients had received substantially large amounts of extract.

DISCUSSION

The question arises whether the precipitate observed represents immune substances other than antigen and specific rabbit serum. That it is probably not reagin is indicated by the fact that no precipitation occurred in sera rich in reagins taken before the hay fever season. It apparently does not represent blocking or thermostable antibody since precipitates appeared in sera of untreated patients in whom no thermostable antibody was otherwise detected. It is presumed, therefore, that the precipitate probably is a measure of circulating antigen, at times in surprisingly large amounts.

The significance of this observation has not yet been evaluated. It would seem to complicate rather than simplify our conceptions of immune phenomena in hay fever. Preliminary studies have revealed that atopic reagins, blocking or thermostable antibody, and antigen may all be present simultaneously in the circulating blood during the hay fever season. That the two antibodies are not neutralized by antigen is readily demonstrable in vitro, and the circumstances that keep them apart are unknown.

It is realized that ragweed antigen, as employed in these experiments, is a mixture of many antigens, and so there are probably many antibodies. Which of the antigens are represented by the precipitate is as yet unknown.

Since antigen apparently remained in the blood streams of some patients whose symptoms continued for some time after the cessation of pollination, one may speculate whether or not the nasal mucosa of these individuals was contacting sufficient pollen extract in the serum to continue symptoms. The problems involved indicate again how complex are the mechanisms involved and how much there is still to be learned about them.

SUMMARY

1. Ragweed antigen in the sera of hay fever patients has been demonstrated by the precipitin test and roughly quantitated in terms of volume of precipitate.

2. A trend was observed wherein the amount of precipitate was roughly proportionate to the severity of symptoms.

3. Correlation between the amount of circulating antigen, thermostable antibody, and reagins, and the relation of these values to the dosage of pollen extract and the pollen count, as well as a more accurate estimate of symptoms, are to be studied.

The authors wish to express appreciation to Dr. Charles H. Eyermann for his kindness in securing many blood samples for this study.

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Original Articles

QUANTITATIVE ESTIMATION OF THE ABSORPTION OF AN INGESTED ALLERGEN*

JOSEPH R. SPIES, PH.D., DORRIS C. CHAMBERS, M.S., HARRY S. BERNTON, M.D., AND HENRY STEVENS, PH.D., WASHINGTON, D. C.

INTRODUCTION

PREVIOUS papers from this laboratory have described the isolation[1, 2] and chemical characterization[3-6] of an allergenic polysaccharidic-protein fraction, CS-1A, from cottonseed, that was immunologically distinct from other allergens[7-8] and antigens[9-11] present in the cottonseed. The object of this paper is to describe a method for the quantitative estimation of the quantities of allergen absorbed from the gastrointestinal tract when CS-1A and defatted cottonseed are ingested. By this method, reactions in passively sensitized sites provide means of comparing the quantities of allergen that enter the circulation as a result of intramuscular injection and of absorption from the gastrointestinal tract. The procedure involves two steps. First, the quantity of CS-1A, introduced intramuscularly, required to incite a positive reaction and also to neutralize the reagins in a site sensitized with serum from a cottonseed-sensitive subject is determined. Second, the quantity of ingested CS-1A or cottonseed that will likewise incite a positive reaction and also neutralize the reagins in a sensitized site is determined under the same experimental conditions. The quantity of allergen which was absorbed can then be estimated by comparing quantities of ingested CS-1A and cottonseed that induce effects at the sensitized sites equivalent to those produced by definite quantities of CS-1A when introduced intramuscularly. The method may be generally applied to allergens from other sources.

Freeman,[12] in 1925, first recorded the observation that ingested egg allergen passes from the digestive tract into the circulatory system. This was shown by excitation of a site, passively sensitized with serum from an egg-sensitive subject, when egg was ingested. Lewis and Grant,[13] at Freeman's suggestion, showed that, upon ingestion of herring, an allergen likewise entered the circulatory system. M. Walzer,[14, 15] working independently, recorded similar observation with both fish and egg allergens. He recognized that the quantity of allergen absorbed upon ingestion of a food was small, but he emphasized the importance to allergists and immunologists of the demonstration that mere traces of unaltered antigen or allergen may pass through the walls of the gastrointestinal tract. Walzer also pointed out that this method, which qualitatively demonstrated absorption, was not of value in determining the actual quantity of allergen absorbed. In 1935, A. Walzer and M. Walzer[16] described a method for determination of the relative quantity of allergen in the circulatory system at intervals after the protein meal. But this method did not determine the

*Contribution from Allergen Investigations, Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture, Washington, D. C.

actual quantity of allergen absorbed. Harten, Gray, Livingston, and Walzer[17] stated that, according to unpublished experiments of Brunner and Baron, when 0.0001 mg. of nitrogen of an unfractionated extract of cottonseed was injected intravenously into man, positive reactions were thereby produced in sites passively sensitized with serum from a cottonseed-sensitive subject. Harten and his co-workers[17] reported that, when this same serum was used to passively sensitize sites on monkeys, intravenous injection of 0.0002 mg. of nitrogen of an unfractionated extract of cottonseed produced positive reactions in the sites. M. Walzer[18] subsequently discussed these and other studies pertaining to this subject.

Demonstration of the absorption of allergen from ingested cottonseed was first reported by Ratner and Gruehl.[19] These authors, as well as M. Walzer,[20] adequately reviewed the historical aspects of the subject of the entry into the circulatory system of unaltered protein from the digestive tract, and therefore no further attention to them is needed here.

BLOOD SERUM

A sufficient quantity of blood serum was collected from a cottonseed-sensitive subject (G. W.) so that all passive transfer tests could be conducted with the same lot. Possible variation in reagin content of the serum was, therefore, limited to the gradual decrease in titer which might occur in storage at 2° to 5° C. during the two-month period of the experiments. The potency of the serum was tested by the method of Coca and Grove.[21] Positive passive transfer reactions were obtained with this serum when used in a dilution of $1:10^2$ but no reaction occurred with a dilution of $1:10^3$.

TEST SUBJECTS

Subjects were selected at random from the obstetric ward at Gallinger Hospital, Washington, D. C. They were tested with CS-1A to demonstrate lack of sensitivity to cottonseed allergen. The tests to be described were conducted just before or within a few days after parturition, an interval when the subjects could be retained under observation for the duration of the tests.

MATERIAL USED

CS-1A.—The procedure used in the isolation of CS-1A has been described in detail elsewhere.[1, 2] CS-1A, which represented about 1 per cent of the defatted cottonseed, contained 11.8 per cent total nitrogen and 39.9 per cent polysaccharidic carbohydrate. A stock solution containing 100 mg. of CS-1A (ash-, water-free basis) in 100 ml. of physiologic salt solution was prepared. This solution was sterilized by heating at 100° C. for fifteen-minute periods on three successive days. Suitable dilutions of this solution, in sterile physiologic salt, were prepared to provide the required concentrations of CS-1A. For ingestion experiments, weighed quantities of CS-1A (ash-, water-free basis) were dissolved in 25 ml. of water.

Defatted Cottonseed.—The cottonseed was prepared by thorough ether extraction of "choice quality," dehulled cottonseed meats carefully hand-picked and ground. The extracted cottonseed was pulverized to a fine powder. Residual ether was removed by heating in an autoclave at 100° C. for fifteen minutes. For the ingestion experiments, weighed quantities of the cottonseed were stirred with enough warm water to form a thin suspension.

DETERMINATION OF THE REACTION-INCITING AND REAGIN-NEUTRALIZING CAPACITIES OF INTRAMUSCULARLY-INJECTED CS-1A

Determinations were made of the quantities of CS-1A required to induce positive reactions in passively sensitized sites and to desensitize the sites to further test with 100 γ* of CS-1A.

By a uniform procedure, a single site on the right upper arm of each subject was sensitized with 0.05 ml. of undiluted serum. After an interval of at least twenty-four hours, 1 ml. of one of several dilutions of CS-1A was injected intramuscularly into the left arm. If the amount of CS-1A injected was sufficient to incite a reaction, itching at the sensitized site developed within a few minutes, and a wheal formed in ten to forty minutes. The maximum diameter of the wheal that developed within sixty minutes after the injection was used for measurement of the reaction.

After an interval of at least twenty-four hours, the sites were tested to determine neutralization of reagins. For this purpose 0.25 ml. of a solution containing 100γ of CS-1A was injected subcutaneously into the right arm 30 to 40 mm. distal to the sensitized site. This technique for testing for neutralization of reagins, rather than injection of the CS-1A solution directly into the sites, was adopted because it eliminated need for a separate control test. Also, false plus-minus reactions owing to trauma of tissue not yet returned to normal were avoided by this indirect injection method. The use of one relatively large dose of CS-1A to test for neutralization was a permissible simplification because the objective of the experiments required only that comparative results be obtained. Therefore the multiple proportion effect[22] in reagin neutralization could be neglected.

TABLE I. QUANTITY OF CS-1A, INTRODUCED INTRAMUSCULARLY, REQUIRED TO INDUCE POSITIVE PASSIVE TRANSFER REACTIONS AND NEUTRALIZE REAGINS

SUBJECT*	INITIAL TEST†		TEST FOR NEUTRALIZATION OF REAGINS§ REACTION (MM.)
	QUANTITY OF CS-1A INJECTED (γ)	REACTION‡ (MM.)	
Z. C.	1	0	15 × 17
O. P.	1	0	15 × 17
E. R.	1	0	40 × 30
L. W.	1	0	16 × 20
A. B.	1	0	25 × 39
E. L.	10	8 × 8	15 × 15
C. M.	10	5 × 5	30 × 20
D. Wh.	10	0	20 × 20
E. B.	10	0	28 × 25
M. R.	100	10 × 10	0
M. B.	100	30 × 30	0
I. P.	100	22 × 22	0
L. S.	100	7 × 10	0
M. T.	100	18 × 15	0
N. B.	100	15 × 15	0
A. Br.	100	18 × 15	0
C. Mc.	100	32 × 32	0
D. Wi.	100	15 × 16	0
M. H.	1,000	14 × 14	0
B. H.	1,000	25 × 19	0
R. J.	1,000	20 × 18	0

*Subjects were uniformly sensitized on the right upper arm with 0.05 ml. of serum from cottonseed-sensitive patient (G.W.).

†The indicated quantity of CS-1A (ash-, water-free basis) in 1 ml. of sterile salt solution was injected intramuscularly in the left arm at least twenty-four hours after sensitization.

‡The numbers refer to the maximum size of the wheal (in millimeters) which formed within sixty minutes after injection of CS-1A.

§Test for neutralization of reagins was uniformly made by subcutaneous injection of 0.25 ml. of a sterile salt solution containing 100γ of CS-1A about 30 to 40 mm. below the sensitive site. The numbers refer to the size of the wheal (in millimeters) which formed within sixty minutes. Test for neutralization was made at least twenty-four hours after the initial test.

*The symbol γ = 0.000001 gram. This symbol, designated "microgram," has been approved by the Committee on Nomenclature, Spelling and Pronunciation of the American Chemical Society (Chem. & Engin. News 18: 491, 1940).

Results of tests to determine the minimum quantities of CS-1A required to induce positive reactions and to neutralize the reagins at the passively sensitized sites are shown in Table I. One microgram of CS-1A was insufficient to produce positive reactions in any of five tests. Ten micrograms induced positive reactions in two out of four tests, but this quantity did not desensitize the sites. One hundred micrograms produced positive reactions in all nine tests and also neutralized every site. One thousand micrograms of CS-1A induced positive reactions in three tests and neutralized the sites in each case.

DETERMINATION OF THE REACTION-INCITING AND REAGIN-NEUTRALIZING CAPACITIES OF INGESTED CS-1A

Determinations were made of the quantities of ingested CS-1A that would be required to incite positive reactions in passively sensitized sites and desensitize the sites.

Sites on the upper right arm of subjects were passively sensitized with 0.05 ml. of serum as before. After an interval of at least twenty-four hours a quantity of CS-1A dissolved in 25 ml. of water was administered orally before breakfast. The container was rinsed with an additional 25 ml. of water, and this rinse solution was also ingested. The maximum diameter of the wheals that formed within ninety minutes after the ingestion was used for measuring the reactions. The sites were tested for neutralization of reagins, following an interval of at least twenty-four hours after the ingestion, by a subcutaneous

TABLE II. QUANTITY OF INGESTED CS-1A REQUIRED TO INDUCE POSITIVE PASSIVE TRANSFER REACTIONS AND NEUTRALIZE REAGINS

SUBJECT*	INITIAL TEST†		TEST FOR NEUTRALIZATION OF REAGINS§
	QUANTITY OF CS-1A INGESTED (MG.)	REACTION‡ (MM.)	REACTION (MM.)
A. D.	50	0	—
G. C.	50	0	25 × 15
B. S.	100	0	22 × 15
G. B.	100	0	23 × 25
D. H.	100	0	22 × 22
D. M.	100	0	20 × 20
C. G.	100	15 × 18	± Redness
C. H.	100	±	16 × 15
E. W.	100	15 × 15	10 × 15
M. S.	200	Itching	24 × 22
L. M.	200	0	16 × 15
A. C.	200	30 × 25	—
I. K.	200	0	10 × 12
R. B.	200	0	18 × 15
R. M.	200	20 × 18	15 × 10
O. B.	200	25 × 18	17 × 20
O. W.	400	Heat, Redness	10 × 7
L. C.	400	25 × 22	0
M. T.	400	15 × 15	0
M. G.	400	11 × 15	0
E. A.	400	Redness	Redness
E. C.	800	20 × 25	0
E. N.	800	20 × 20	0
B. J.	800	20 × 22	0
W. S.	800	20 × 15	0
T. W.	800	15 × 13	9 × 7
V. B.	1,000	25 × 24	0

*Subjects were uniformly sensitized on the right upper arm with 0.05 ml. of serum from cottonseed-sensitive patient (G.W.).

†The indicated quantity (milligrams) of CS-1A (ash-, water-free basis) dissolved in 25 ml. of water was given orally before breakfast at least twenty-four hours after sensitization.

‡The numbers refer to the maximum size of the wheal in millimeter) which formed within ninety minutes after ingestion of the CS-1A.

§Test for neutralization of reagins was made at least twenty-four hours after the ingestion of CS-1A.

injection of 0.25 ml. of a solution containing 100γ of CS-1A by a method similar to that used in the intramuscular tests. Results of this series of tests are shown in Table II. These results, as would be expected, show more variability than those obtained by the intramuscular injection of CS-1A.

Fifty milligrams of ingested CS-1A induced no positive reactions in two tests. One hundred milligrams of ingested CS-1A produced two positive reactions out of seven tests, but in no case was the site desensitized. Two hundred milligrams of CS-1A caused four positive reactions out of seven tests, but again the sites were not neutralized. Four hundred milligrams of CS-1A produced reactions in all tests, and three out of the five sites were desensitized. When 800 mg. of CS-1A were ingested, positive reactions were obtained in all five tests and all sites but one were neutralized. In one test, ingestion of 1,000 mg. of CS-1A produced a reaction, and the site was desensitized. Additional ingestion tests, though desirable, were not conducted owing to the limited quantity of CS-1A available.

DETERMINATION OF THE REACTION-INCITING AND REAGIN-NEUTRALIZING CAPACITIES OF INGESTED COTTONSEED

The quantities of defatted cottonseed necessary to incite positive reactions in passively sensitized sites and to desensitize the sites were determined by the same procedure as employed in the CS-1A ingestion experiments. The powdered cottonseed was given orally in a warm, watery suspension before breakfast. The maximum diameter of the wheal that formed within ninety-minutes after the ingestion was used for measuring the reaction. The sites were tested for neutralization of reagins after an interval of at least twenty-four hours by a subcutaneous injection of 0.25 ml. of a solution containing 100γ of CS-1A at a point 30 to 40 mm. distal to the sensitized site. Results of this series of tests are shown in Table III. One gram of ingested cottonseed induced a positive reaction in one out of three tests, but the sites were not neutralized. Dosage levels of 2, 5, 10, and 20 Gm. of ingested cottonseed caused positive reactions in every test. The sites were neutralized in all (four) tests, however, only at the 20-Gm. dosage level.

TABLE III. QUANTITY OF INGESTED COTTONSEED REQUIRED TO INDUCE POSITIVE PASSIVE TRANSFER REACTIONS AND NEUTRALIZE REAGINS

	INITIAL TEST†		TEST FOR NEUTRALIZATION OF REAGINS§
SUBJECT*	QUANTITY OF COTTONSEED INGESTED (GM.)	REACTION‡ (MM.)	REACTION (MM.)
J. B.	1	28 × 28	Redness, Heat
C. D.	1	0	20 × 16
E. B.	1	0	22 × 20
M. R.	2	20 × 15	25 × 20
R. W.	2	Heat	20 × 14
R. L.	5	20 × 20	28 × 22
O. H.	5	Redness	18 × 16
A. F.	5	11 × 14	24 × 20
C. S.	10	10 × 8	14 × 13
D. S.	10	Redness	20 × 20
H. W.	20	22 × 24	0
J. M.	20	18 × 18	0
E. E.	20	23 × 22	0
W. M.	20	28 × 30	0

*Subjects were uniformly sensitized on the right upper arm with 0.05 ml. of serum from cottonseed-sensitive patient (G.W.).

†The indicated quantity (grams) of defatted cottonseed, suspended in water, was given orally before breakfast at least twenty-four hours after sensitization.

‡The numbers refer to the maximum size of the wheal (in millimeters) which formed within ninety minutes after ingestion of CS-1A.

§Test for neutralization of reagins was made at least twenty-four hours after ingestion of the cottonseed.

DISCUSSION

The method described for the quantitative estimation of the absorption of allergen from ingested CS-1A and defatted cottonseed is based on the principle that reagins in passively sensitized sites are incited to wheal formation and are also neutralized by definite quantities of an allergen. This quantitative relationship is, however, reliable only if the conditions of the tests are rigidly standardized. In this study, effort has been made to reduce variable factors to a minimum consistent with practicable procedure. It is recognized that the results may be influenced by some variables that cannot be evaluated without further study. It has been assumed that, with regard to the total effect of the allergen on the sensitized sites, the intramuscular route of entry of allergen into the circulation is comparable with entry by absorption. The effect on reagin neutralization of differences in the concentration attained by the allergen in the circulation as a result of the more rapid intramuscular administration or as a result of variable rates of absorption in different subjects is not known. Rapid absorption may neutralize the sensitized site more effectively than gradual absorption, even though the total quantity of allergen absorbed in the latter case may exceed that in the former. Conversely, slow absorption may be more effective in reagin neutralization than rapid absorption. Also rapid absorption of an allergen may incite reaction in a sensitized site, whereas slow absorption of an equal or even greater quantity of allergen would not cause a reaction. However, these factors would not be expected to have the same effect in modifying the percentage of absorption as determined by reaction-inciting or reagin-neutralizing capacity. As shown later, the percentage of absorption as determined by both reaction-inciting and reagin-neutralizing capacities agree as closely as could be expected from available data. Therefore, these unknown factors probably do not have undue influence on the results.

Retention of the property of specific reaction of allergen with reagins in passively sensitized sites is generally regarded as evidence of the unaltered nature of the allergen.[20]. The possibility is recognized, however, that exposure of ingested allergen to the action of digestive enzymes, even briefly, might cause slight alterations in structure of the absorbed allergen which could decrease without destroying the reagin-reacting properties of the allergen.[4, 23]

In the procedure employed, the minimal quantities of allergen required to produce equivalent reactions in the sensitized sites are determined when the allergen is administered orally and parenterally. Comparison of the results affords a basis for measuring indirectly the quantity of allergen that is absorbed from measured quantities of ingesta. Two criteria were available for comparison of the effect of CS-1A on the sensitized site when introduced either intramuscularly or orally. These criteria were determinations of the minimum amount of CS-1A which incited reaction in the sensitized site and the quantity which neutralized the site. The results in Tables I and II show that 10 γ of CS-1A introduced intramuscularly were approximately equivalent to 100 mg. of CS-1A given orally for the incitation of reactions. The ratio of intramuscular to oral administration in the induction of reactions is therefore 1:10,000. On this basis, it may be deduced that 0.01 per cent of the allergen is absorbed when 100 mg. of CS-1A are ingested. The reagin-neutralizing power of 100 γ of CS-1A given intramuscularly was approximately equivalent to that of 800 mg. of CS-1A given orally. The ratio of reagin-neutralizing power of intramuscularly to orally administered CS-1A is therefore 1:8,000. According to this

method of determination, 0.013 per cent of the allergen is absorbed when 800 mg. of CS-1A are ingested. The calculations from the two criteria are in good agreement when the recognized variability of subjects and the comparatively small number of cases studies are considered. It is recognized that the percentage of absorption may vary with the size of the dose ingested. However, this point cannot be determined from available data.

An allergenic component of CS-1A is readily dialyzable.[1, 11] This may explain why the CS-1A specific allergen of cottonseed passes through the walls of the gastrointestinal tract. It would be of interest to investigate the absorption of a nondialyzable allergen from cottonseed.[8]

The allergenic fraction CS-1A represents at least 1.1 per cent of the defatted cottonseed on the basis of actual isolation.[1, 2] However, it is recognized that this is a minimal value because the objective for isolating CS-1A was to obtain the allergen immunologically distinct from other allergens in the cottonseed rather than to effect a quantitative separation of allergen. That CS-1A is not chemically homogeneous has been recorded previously, but the proportion of allergen present in either CS-1A or cottonseed, from which this fraction was isolated, has not been determined. In the present study, the allergic response of sites passively sensitized with serum from a cottonseed-sensitive subject to ingested CS-1A and defatted cottonseed provides a means for estimating the relative concentration of allergen in CS-1A and cottonseed. This comparison is made on the basis of determination of the minimal quantities of ingested CS-1A and cottonseed that will incite positive reactions in passively sensitized sites and that will neutralize the reagins in these sites. The following factors, which, however, cannot be evaluated by available data, must be considered in relation to this method of determining relative concentration of allergen in CS-1A and cottonseed. First, the CS-1A was administered orally in water *solution,* whereas the cottonseed was given orally as a watery *suspension.* The possibility is recognized that allergen in CS-1A might therefore be more readily available for diffusion from the gastrointestinal tract than allergen in the cottonseed suspension. Whether or not the availability of allergen for diffusion in the suspension of cottonseed is a critical factor cannot be determined from available data. Second, the sensitizing serum used in this study contained reagins specific both for CS-1A and another allergen, or other allergens, present in the seed. Although the nature of the unidentified allergen or allergens has been studied previously,[1, 8] as yet insufficient facts are available to decide whether or not these unidentified allergens contributed to the initial incitation of the reactions under the conditions of this experiment. The possibility is therefore recognized that the positive passive transfer reactions obtained with the cottonseed might result from a summation of reactions induced by CS-1A and the other allergens. This difficulty could be avoided by using serum from a Type II cottonseed-sensitive subject; that is, one sensitive to CS-1A alone.[1, 7, 8] However, this would have necessitated redetermination of the data for CS-1A in Table II. This has not been possible under present circumstances.

The capacity of ingested cottonseed to neutralize reagins specific for CS-1A, however, is comparable with neutralizing power of CS-1A because CS-1A is immunologically distinct from the unidentified allergens of the cottonseed. Results in Tables II and III show that the CS-1A-reagin-neutralizing power of 800 mg. of ingested CS-1A was approximately equivalent to that of 20 Gm. of ingested cottonseed. Therefore, it can be estimated that CS-1A contains a concentration of this allergen approximately twenty-five times as great as that in defatted cottonseed.

SUMMARY

1. A method is described for the quantitative estimation of the approximate quantities of cottonseed allergen absorbed from the digestive tract when CS-1A and cottonseed are ingested. The method may be generally applied to other allergens and has potential applicability in fundamental studies of the diffusibility of allergens from the gastrointestinal tract.

2. Ten micrograms of CS-1A introduced intramuscularly were approximately equivalent to 100,000 γ of ingested CS-1A in capacity to incite passive-transfer reactions. On this basis, when 100 mg. of CS-1A were ingested, 0.01 per cent of the allergenic fraction was absorbed.

3. One hundred micrograms of CS-1A introduced intramuscularly were approximately equivalent to 800,000 γ of ingested CS-1A in reagin-neutralizing power. According to this criterion, when 800 mg. of CS-1A were ingested, 0.013 per cent of the allergenic fraction was absorbed.

4. One hundred micrograms of CS-1A introduced intramuscularly were approximately equivalent to 20,000,000 γ of ingested cottonseed in reagin-neutralizing capacity.

5. Eight-tenths of a gram of ingested CS-1A was approximately equivalent to 20 Gm. of ingested cottonseed in reagin-neutralizing power.

6. The method described may be applicable to the determination of the relative concentration of an allergen in two substances by comparing the quantities of the ingested substances required to induce equivalent effects in passively sensitized sites. By this method it was estimated that CS-1A contains a concentration of allergen approximately twenty-five times as great as defatted cottonseed.

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A QUANTITATIVE STUDY OF THE RELATION OF SYNTHETIC 3-PENTADECYL CATECHOL TO HYPERSENSITIVENESS TO RHUS TOXICODENDRON (POISON IVY) AS SHOWN BY THE PATCH TEST

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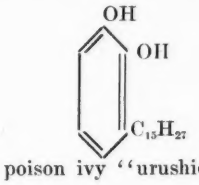
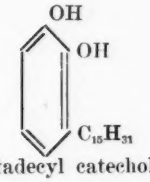
PERSONS sensitive to the leaves or extract of *Rhus toxicodendron* (poison ivy), as shown by the technique of patch testing, exhibit also constant group specific reactions to synthetic 3-pentadecyl catechol.[1] Thus, in a group of fifty unselected persons, of which only one was suffering from active poison ivy dermatitis at the time of testing, twenty-nine subjects gave negative responses to patch tests with ground poison ivy leaves or extract or both, as well as to 3-pentadecyl catechol and other related derivatives of catechol applied in a concentration of 1 per cent in acetone. In the remaining twenty-one subjects, positive reactions were elicited by the ground poison ivy leaves or extract or both, and all of these persons showed positive responses to a 1 per cent solution of 3-pentadecyl catechol in acetone (1 Gm. per 100 c.c. of acetone).[1]

The active ingredient causing poison ivy dermatitis is a catechol compound with an unsaturated normal side chain of fifteen carbon atoms in the 3-position, the side chain having an average of two double bonds in positions as yet undetermined.[2] On the other hand, synthetic 3-pentadecyl catechol differs from the active ingredient in the poison ivy plant in that the side chain is fully saturated. The following formulas will illustrate this difference.



poison ivy "urushiol"



3-pentadecyl catechol

In view of the uniformly positive group specific reactions elicited by 3-pentadecyl catechol in persons sensitive to poison ivy materials, as observed in our previous studies,[1] it seemed desirable to investigate the reactivity of 3-pentadecyl catechol from a quantitative point of view. The results observed in twenty-one cases are given in Table I.

The twenty-one selected persons were all sensitive to *Rhus toxicodendron*. This group contained ten cases showing active or receding lesions of poison ivy dermatitis at the time of testing. Of the twenty-one persons, twenty showed positive patch tests to the ground poison ivy leaves or to an extract (nineteen to the former, one to the latter); the remaining case, which was not tested with either of these two materials, had been seen previously in an attack of poison ivy dermatitis and, at the time of testing, had returned with a fresh recurrence of the condition in typical form. All subjects gave positive patch tests to synthetic 3-pentadecyl catechol in concentrations of 1 per cent, or less, in acetone. Adding these data to those previously reported, it will be

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TABLE I*

CASE	REACTIONS: RHUS LEAVES 48 HR.	RHUS LEAVES 96 HR.	3-PENTADECYL CATECHOL 1% 48 HR.	1% 96 HR.	0.1% 48 HR.	0.1% 96 HR.	0.01% 48 HR.	0.01% 96 HR.	0.001% 48 HR.	0.001% 96 HR.	0.0001% 48 HR.	0.0001% 96 HR.	CONDITION AT TIME OF TESTING	REMARKS ON PATCH TEST
1	++		++ (+)	+++ (+)	±	+++	neg.	++	neg.	neg.	neg.	neg.	Dermatitis venenata (rayon lining)	
2	++		+++	+++ (+)	+ (+)	+++	neg.	+++	neg.	++	neg.	neg.	Dermatitis venenata probably due to medicaments applied	
3	+ (+)		++	+++ (+)	±	+++	neg.	++ (+)	neg.	neg.	neg.	neg.	Dermatitis venenata due to perfumed shampoo	
4	+++				+++ (+)	+++ (+)	+ (+)	+++	neg.	+	neg.	neg.	Poison ivy dermatitis	
5	+++†				+	+++ (+)	±	+++	neg.	–neg.	neg.	–neg.	Senile pruritis	
6	+++		++++		++ (+)		+ (+)		neg.		neg.		Chronic eczema due to cement	
7	++ (+)		+++ (+)	++ (+)	++ (+)	++ (+)	±	+ (+)	neg.	+	neg.	±	Probably poison ivy dermatitis	
8	++		+++		++ (+)		++		±		neg.		No rash	Patches on skin only 24 hr.
9	+	++	++ (+)	+++	+	+++	±	++ (+)	neg.	+	neg.	neg.	Poison ivy dermatitis	
10	+	±	++	+	+ (+)	+	±	±	neg.	neg.	neg.	neg.	Infected bites on legs?	
11	++	++	+++	++	++ (+)	+ (+)	++	+	neg.	neg.	neg.	neg.	Household eczema of fingers	
12	++		++ (+)		+ (+)		neg.		neg.		neg.		Household eczema of hands	
13	neg.	+++‡	neg.	++++ (+)	neg.	++++	neg.	+++	neg.	+ (+)	neg.	+ (+)	Poison ivy dermatitis	Negative at 48 hr. Delayed positive at 60 hr.
14	++				+++ (+)		++		++		±		Atopic dermatitis and hay fever	
15	++ (+)						++		neg.		neg.		Poison ivy dermatitis in fading stage	
16	+++						+ (+)		neg.		neg.		Neurodermatitis	
17	+ (+)	++					+ (+)	+++	neg.	neg.	neg.	neg.	Poison ivy dermatitis	
18							+++	++ (+)	+ (+)	+ (+)	neg.	neg.	Poison ivy dermatitis	
19	+++						+++ (+)		+++		+ (+)		Poison ivy dermatitis	
20	+	+++					+ (+)	+++ (+)	neg.	++	neg.	+ (+)	Poison ivy dermatitis	Mild focal reaction on thighs
21	++ (+)						+++		+ (+)		neg.		Poison ivy dermatitis in fading stage	

*See Reference 1 for method of grading.
†Extract used.
‡Sixty-hour reading.

seen that forty-two persons sensitive to the poison ivy plant, as shown by the patch test, were all likewise sensitive to synthetic 3-pentadecyl catechol.

An analysis of the quantitative data in Table I shows that 3-pentadecyl catechol in 1 per cent concentration in acetone (eleven subjects) elicited fairly intense reactions which exceeded those exhibited by the ground poison ivy leaves. Comparing the initial responses at forty-eight hours, a concentration of 0.1 per cent 3-pentadecyl catechol (fourteen subjects) showed more pronounced reactions than the poison ivy leaves in six persons, about the same in two, and less intense in six. In those instances in which the responses could be observed at ninety-six hours, the majority of reactions to this concentration of 3-pentadecyl catechol became more pronounced. Using a concentration of 0.01 per cent 3-pentadecyl catechol (twenty-one subjects), all except one instance exhibited definite positive reactions; however, in some cases the responses were truly delayed until seventy-two to ninety-six hours. In the case of 0.001 per cent 3-pentadecyl catechol (twenty-one subjects), only seven showed unequivocal positive responses and almost one-half were delayed to the third or fourth day. Only three persons in twenty-one tested with 0.0001 per cent 3-pentadecyl catechol showed positive reactions. These responses were mild and were delayed in two of the three cases.

These data indicate that a concentration of 0.1 per cent 3-pentadecyl catechol in acetone represents, generally, the optimal strength for testing in order to avoid unduly severe reactions; however, an observation period of ninety-six hours is requisite for final evaluation. Although it is possible that the use of a somewhat higher concentration (as 0.5 per cent) might eliminate a number of the delayed responses, it should be pointed out that there were instances in which patients showed a delayed reaction to even higher concentrations. Thus, Case 13 was an example of a sixty-hour reactor. All the patch sites in this patient were negative at forty-eight hours, including 1 per cent 3-pentadecyl catechol, whereas intensely positive reactions appeared at sixty hours. It is possible, also, that the use of 0.1 per cent concentration may, in rare cases, fail to detect the mildly sensitive person. For example, in an additional group of twenty instances showing positive responses to 1 per cent 3-pentadecyl catechol, we encountered one exceptional case in which the reaction to 0.1 per cent concentration was doubtfully positive. Thus, among forty-one subjects exhibiting positive reactions to 1 per cent 3-pentadecyl catechol, only one failed to show a definitely positive response to a 0.1 per cent concentration of this substance.

Synthetic 3-pentadecyl catechol in suitable concentration may, therefore, apparently replace ground poison ivy leaves or extract in testing for hypersensitiveness to *Rhus toxicodendron* and probably, also, related plants. Our present procedure is to apply a 0.1 per cent concentration for forty-eight hours, with rereading on the fourth or fifth day. If the result is negative, the patient is tested with a 1 per cent concentration in order to detect the mildly sensitive case. Although it is possible that, in rare cases, the hypersensitiveness to the poison ivy plant may be restricted to the unsaturated active ingredient alone, without any group reactions to related chemical compounds, thus far this has not been encountered in the concentrations used. These data illustrate well, therefore, the point that group specific reactions may be used to detect hypersensitiveness to a closely related allergen, and this principle has important applications in evaluating hypersensitiveness to other members of the *Anacardiaceae* family.[3] Thus, patch tests with 3-pentadecyl catechol may be carried out on the personnel of industries handling or manufacturing products derived

*See Reference 1 for method of grading.
†Extract used.
‡Sixty-hour reading.

from trees of the *Anacardiaceae* family. As an example one may mention the industry in this country of manufacturing commercially valuable resins and plastics from cashew nut shell liquid. The shell liquid is a powerful irritant having on many people an effect not dissimilar to that of poison ivy. The determination of hypersensitivity by patch testing with 3-pentadecyl catechol could be used to good advantage in selecting personnel for such industries.

Many "poisonous" members of the *Anacardiaceae* family are found in the Far East and the islands of the Southwest Pacific. From the military point of view, it might be a matter of considerable importance to our Armed Forces to know the sensitivity of its personnel to the active ingredients of these plants.

At present the use of ground poison ivy leaves or an extract of the plant entails the disagreeable task of gathering the plant. More important, the concentration of active ingredient seems to fluctuate from time to time and from specimen to specimen, as shown by biologic tests, and there is no available direct method of determining this often variable concentration of active ingredient. The use of 3-pentadecyl catechol, on the other hand, offers several distinct advantages. It is readily synthesized in a highly pure state,[4] so that test solutions of known concentration may be prepared and standardized easily. Likewise, such solutions are free of the many extraneous materials undoubtedly present in commercial extracts, notably nitrogenous substances which may introduce other complications. Furthermore, in view of our observations that unsaturated phenolic compounds are not only more reactive biologically than their saturated analogues, but are, likewise, much less stable chemically, there is reason to believe that 3-pentadecyl catechol would be much more convenient to handle than the pure unsaturated active ingredient of poison ivy. Our experience indicates that 3-pentadecyl catechol, even when applied in 1 per cent concentration, is apparently not a very intense sensitizer per se.* Finally, it may be noted that the use of 3-pentadecyl catechol in a suitable vehicle and concentration might provide a method of attempting desensitization with definite known concentrations of potent substance.

The data presented constitute additional proof that proteins or nitrogenous compounds occurring in the plant or plant extracts play no direct part in the causation of poison ivy dermatitis. However, it seems possible that the catechol compounds combine with proteins in the skin in the manner postulated by Landsteiner's hapten theory.

SUMMARY

1. Sixty-two persons sensitive to the poison ivy plant were found to be sensitive to synthetic 3-pentadecyl catechol in concentrations of 1 per cent, or less, in acetone. This substance is the saturated analogue of the active ingredient causing poison ivy dermatitis.

2. Quantitative studies in twenty-one subjects sensitive to poison ivy showed that a 0.1 per cent concentration of 3-pentadecyl catechol in acetone is suitable to detect those sensitive to the poison ivy plant, and probably also, related plants; however, for final evaluation a period of ninety-six hours of observation is requisite. The advantage of using this concentration is that severe reactions are eliminated for the most part. There are occasional instances in which, after

*There is a fundamental distinction between a positive patch test to synthetic 3-pentadecyl catechol in persons already sensitive to the poison ivy plant and the ability of 3-pentadecyl catechol to induce sensitization in persons previously not sensitive to this substance or to the poison ivy or related plants. Thus, among thirty-four persons who showed negative responses to 1 per cent 3-pentadecyl catechol in a first patch test, one became mildly sensitive to this substance on a retest done about ten days or two weeks later. It is interesting that in this same patient a retest with ground poison ivy leaves remained negative.

ninety-six hours, a 1 per cent concentration may be used to reveal the exceptionally mildly sensitive patient who fails to react to a 0.1 per cent concentration.

3. The advantages of using synthetic 3-pentadecyl catechol as a replacement for ground poison ivy leaves or extract in testing for hypersensitiveness to *Rhus toxicodendron* have been pointed out. It is suggested that in a suitable vehicle and concentration this substance may be used in an attempt to desensitize persons sensitive to the poison ivy plant and its congeners.

4. The principle of group specific reactions is amply illustrated in the case of 3-pentadecyl catechol in its relation to the active ingredient in poison ivy dermatitis.

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SPONTANEOUS MEDIASTINAL AND SUBCUTANEOUS EMPHYSEMA COMPLICATING BRONCHIAL ASTHMA

Report of an Additional Case and Analysis of Twenty-Five Previously Reported Cases*

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Macklin and Macklin[1] in their essay, "Pulmonic Interstitial Emphysema," included such conditions as mediastinal emphysema, or pneumomediastinum, and subcutaneous emphysema. They have shown by their experiments that these conditions originate from an initial pulmonary interstitial emphysema. In a more recent publication,[2] these authors stated that the essential factor in pulmonic interstitial emphysema is a pressure gradient between the air in the alveolus and the connective tissue underneath, leading to a rupture of the base of the "marginal" type of alveolus. The air seeps through multiple small ruptures in the alveolar bases and enters the pulmonic interstitial tissue. This initial phase of pulmonary interstitial emphysema is seldom recognized clinically. The pulmonic blood vessels underlying the alveolar bases become compressed, and the arterial and venous circulation is impeded. The air then travels along the vascular sheaths to the mediastinum. The mediastinum becomes distended and through pressure on the heart and great vessels produces further embarrassment of the circulation. This point of invasion of the air, known as mediastinal emphysema, is now being recognized with more frequency. Macklin and Macklin have suggested that, in spontaneous pneumothorax, the air reaches the pleural cavity through the mediastinum. It is possible that in some cases air may travel along the interstitial bands of the

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lung to the pleura and form a subpleural bleb which may rupture. However, this has never been demonstrated. Before the Macklins' intensive study, it was thought that the air in the pleural cavity was due to a rupture of an emphysematous bleb and to minute pleural tears produced by the pull of adhesions. From the mediastinum the air may spread, producing pneumopreccordium, interstitial emphysema of the opposite lung due to the backing up of air from the mediastinum, pneumoretroperitoneum, or it may extend along the carotid perivascular sheaths and enter the subcutaneous tissues of the neck and head. The air may also extend to the groin or leg. Such extensions, Macklin and Macklin[1] observed, had a tendency to relieve mediastinal circulatory distress.

Spontaneous mediastinal and subcutaneous emphysema are much more prevalent than is supposed. It is impossible here to mention all the reports on this condition in the literature. However, references will be given to a few of the many reports. This complication has occurred in influenza,[3] pneumonia,[4] pulmonary tuberculosis,[5] diphtheria,[6] after trauma to the chest,[7] by lung blast from explosions,[8] and following too abrupt decompression in leaving caissons or escaping from submarines.[9] It has also been reported to have occurred in individuals who held their breath while lifting heavy weights,[10] during delivery,[11] straining at stool,[12] congenital stenosis of the larynx,[13] during violent coughing spells,[14] following intratrachial anesthesia,[15] or in blowing against an obstruction.[16]

Torrey and Grosch[3] reported a group of patients in the influenza epidemic of 1918 to 1919 who had dyspnea, cyanosis, fixation of the chest in the position of maximal inspiration with scarcely any tidal flow of air, and retrosternal pain. These patients usually died, and at autopsy there was not enough involvement of the lung to explain the marked respiratory distress. Areas of consolidation with other areas of compensatory emphysema were seen and there were often numerous blebs, usually unruptured, beneath the pleura. Several of the practically moribund patients showed sudden improvement; the cyanosis lessened; the breathing became much easier, and they usually went on to recovery. The condition which seemed to explain this sudden improvement was the appearance of subcutaneous emphysema of the neck and face. The simultaneous appearance of pneumothorax and subcutaneous emphysema in some of the patients was interpreted by Berkley and Coffen[16] as being dependent upon a single cause, namely, air in the mediastinum.

As described by Hamman[17] spontaneous mediastinal emphysema is best diagnosed by the combination of substernal pain, a curious "crunching" sound heard over the heart in systole, roentgen evidence of air in the mediastinum, and sometimes an escape of air into the subcutaneous tissues of the neck producing a subcutaneous emphysema. The audible "crunching" sound is pathognomonic of air in the anterior mediastinum, but its absence does not rule out the presence of air in other parts of the mediastinum. According to Hamman the most convincing picture is seen in the lateral roentgenogram when the tissues between the heart and the anterior chest wall are infiltrated with air. In its absence one must look for evidence of air in the mediastinum on the anterior-posterior chest film. The evidence consists of a sharp and distinct line running parallel to the border of the heart. However, the diagnosis is established by the presence of air in the subcutaneous tissues of the neck. Air in the neck may be apparent on an x-ray film before it is possible to detect it clinically.

Subcutaneous emphysema occurring as a complication in bronchial asthma is rare. A careful search into the literature for the occurrence of subcutaneous emphysema complicating bronchial asthma has revealed twenty-five such instances (Table I). Rosenberg and Rosenberg,[18] have collected seventeen cases from the literature and added one of their own in 1938. Seven more have been reported since, and the present case brings the total to twenty-six. With the exception of one of Dietrich's[19] cases, there was no mention of roentgenographic evidence of mediastinal emphysema in any of the cases reported.

TABLE I. CASES OF SUBCUTANEOUS EMPHYSEMA COMPLICATING BRONCHIAL ASTHMA

AUTHOR	AGE (YRS.)	SEX	DURATION OF ASTHMA	DURATION OF EMPHYSEMA (DAYS)	RESULT
1. Knott[20]	5	F	Not given	21	Recovered
2. Watson[21]	18	F	Since childhood	9	Recovered
3. Calverly[22]	17	M	11 yrs.	4	Recovered
4. Whitby[23]	25	M	Since boyhood	The emphysema disappeared gradually	Recovered
5. Kahn[24]	8	F	6 yrs.	10	Recovered
6. MacDermott[25]	22	M	6 yrs.	5 to 6	Recovered
7. Scheltema[26]	30	M	First attack	7	Recovered
8. Artagaveytia and Zanzi[27]	18	M	Since infancy	8	Recovered
9. Scremini and Berro[28]	Not given	F	Not given	"Few"	Recovered
10. Mourigan and Cervino[29]	21	F	Since childhood	2	Recovered
11. Kruysveldt[30]	22	F	Attacks of shortness of breath since childhood	14	Recovered
12. Davidson[31]	9	F	8 yrs.	7	Recovered
13. Pastorino[32]	7	F	Not given	6 to 7	Recovered
14. Pastorino[32]	14	M	Since childhood	10	Recovered
15. Sheldon and Robinson[33]	16	M	1 yr.	4	Recovered
16. Kirsner[34]	38	M	First attack	20	Recovered
17. Bridge[35]	6	M	3 yrs.	6	Recovered
18. Dietrich[19]	5	F	2 yrs.	6	Recovered
19. Dietrich[19]	7	M	5 yrs.	7	Recovered
20. Rosenberg and Rosenberg[18]	3	F	Prior to 1 yr. of age	12	Recovered
21. Van Fleet, Miller, and Scott[36]	3	F	Since infancy	?	Recovered
22. Van Fleet, Miller, and Scott[36]	3	M	2 yrs.	10	Recovered
23. Van Fleet, Miller, and Scott[36]	28	M	7 yrs. Second attack one year later	9	Recovered
24. Van Fleet, Miller, and Scott[36]	19	F	17 yrs.	13	Recovered
25. Skinner[37]	10	?	3 yrs.	10	Recovered
26. Schwartz	24	M	21 yrs.	9	Recovered

CASE REPORT

A 24-year-old Navy yard worker was admitted to the medical service of The Long Island College Hospital, on Nov. 7, 1944, with chief complaints of severe dyspnea, cough, and wheezing.

Past History.—He had eczema at the age of 2, and repeated asthmatic attacks since the age of 3 years. He was tested for sensitivity to the common allergens in 1939, and showed the following reactions: feathers, 2 plus; cottonseed, 3 plus; dog dander, 2 plus; horse dander, 4 plus; flaxseed, 1 plus; tobacco, 2 plus; house dust, 3 plus; giant and dwarf ragweed, 3 plus; codfish, 3 plus; salmon, 3 plus; peanut, 2 plus; coffee, 2 plus; corn, 2 plus; pea, 2 plus; string bean, 3 plus; lima bean, 2 plus; asparagus, 2 plus; and peach, 3 plus. With absolute avoidance of all substances that gave positive reactions, and desensitization with ragweed and house dust extracts, the patient was free from asthmatic attacks from October, 1939, until about one week previous to admission to the hospital, excepting severe asthma, generalized urticaria, and angioneurotic edema that occurred in June, 1941, following ingestion of salmon. There was no evidence of chronic sinusitis or pulmonary disease. A system review revealed no other significant past history.

Family History.—His mother also has asthma.

Present Illness.—One week prior to the patient's admission to the hospital, an asthmatic attack developed and the patient felt it was ushered in by a "cold." This attack, and subsequent ones which recurred every night for about one week, were relieved by ephedrine. Twenty-four hours previous to admission, after inhaling sulfur dioxide fumes escaping from a leaking refrigerator, he suddenly developed a severe attack of difficult breathing, coughing, and wheezing. Several doses of ephedrine did not afford relief. Repeated injections of adrenalin, intravenous aminophylline, and oxygen inhalation also failed to give any relief. In spite of all therapeutic measures the dyspnea became more marked, and the patient became cyanotic. The dyspnea was so severe and the general condition so alarming that death seemed a possibility.

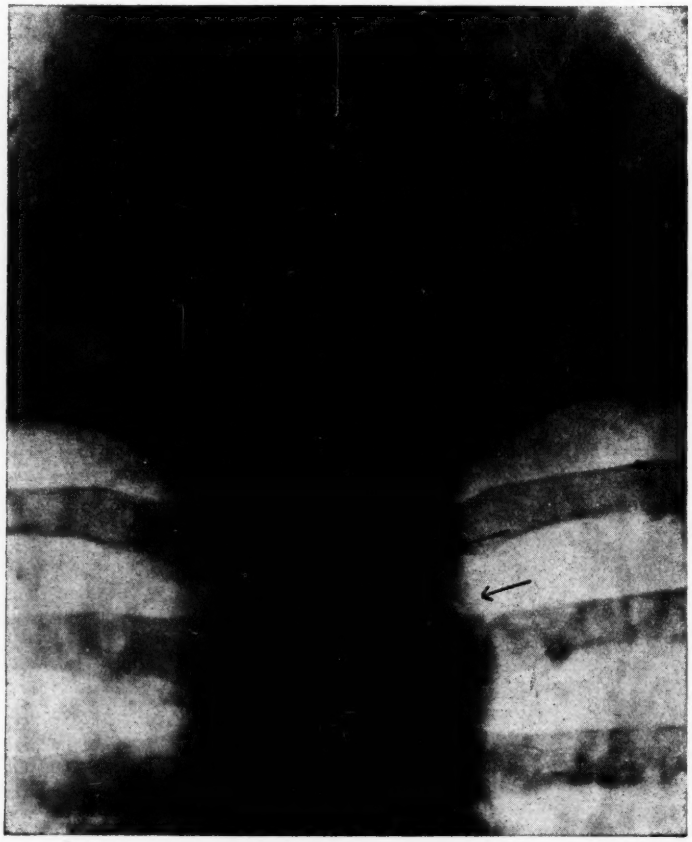

Fig. 1.—Roentgenogram of the chest showing air in the mediastinum.

Physical Examination.—Temperature was 101.4° F.; pulse, 110; respiration, 28; and the blood pressure, 120/78. Examination showed a well-developed and well-nourished male in considerable respiratory distress. Cyanosis was marked. The eyes and ears were negative. The nasal mucous membrane was red and edematous and the pharynx moderately injected. The trachea was in the midline, and on the day of admission there was no evidence of the presence of subcutaneous emphysema. Respirations were labored and it appeared that the chest was fixed in the position of maximal inspiration. No difference was noted between the right and left sides of the chest. The percussion note was hyperresonant throughout. Breath sounds were wheezing in type and many sibilant and sonorous râles were audible during the expiratory phase. Examination of the heart revealed a peculiar "leathery" sound, audible over the entire precordium during systole.

Laboratory Examinations.—Urine: negative throughout; blood count: red cells, 4,450,000; hemoglobin, 15 Gm.; white cells, 25,600; polymorphonuclear forms, 86 per cent; lymphocytes, 13 per cent; and eosinophiles, 1 per cent; suptum: no acid-fast bacilli in direct smear; culture: moderate numbers of hemolytic streptococcic and pneumonocci which did not react to type-specific sera 1 to 32; sedimentation rate: 30 mm. per hour; electrocardio-

gram was normal throughout; roentgenogram of chest on the day following entry showed evidence of mediastinal and subcutaneous emphysema. There was no pneumothorax or pneumonia (Figs. 1 and 2).

Clinical Course.—The morning following admission the patient complained of a slight sensation of pressure in the neck on turning his head. At that time there was clinical evidence of subcutaneous emphysema of the neck. With the appearance of this, the patient's general condition improved. Respirations became easier and the cyanosis disappeared. The subcutaneous emphysema spread and gradually involved the entire neck region up to both ears and over the clavicles to about the second rib on both sides. The temperature dropped to normal on the third day. The peculiar "leathery" sound, audible over the precordium during systole on the day of admission, was present for several hours; then disappeared and did not reappear. The wheezing in the chest disappeared on the sixth day. The duration of the subcutaneous emphysema was nine days, and the patient was discharged on the sixteenth day.

Treatment.—Eight minums of adrenalin hydrochloride (1:1,000) subcutaneously and intravenous injections of 7½ grains of aminophylline gave no relief from the dyspnea and cyanosis previous to the presence of subcutaneous emphysema in the tissues of the neck. The treatment also consisted of oxygen inhalation and the intramuscular administration of 20,000 units of penicillin every four hours for five days. After the appearance of the subcutaneous emphysema the residual wheezing in the chest was relieved by adrenalin.

Fig. 2.—Roentgenogram showing the presence of air in the soft tissues of the neck.

DISCUSSION

In practically all the cases reported, the emphysema was first noted in the neck and spread to the face and chest. In several, the emphysema also spread to the upper extremities and rarely to the abdomen and thighs. The subcutaneous emphysema lasted from two days to three weeks, with an average duration of nine days. In two cases[26, 34] the subcutaneous emphysema occurred during the first asthmatic attack. One of the four cases reported by Van Fleet, Miller, and Scott had a recurrence of subcutaneous emphysema during an asthmatic attack one year later. There were no recurrences in any of the other cases reported despite frequent subsequent attacks of bronchial asthma. Dyspnea and cyanosis were the most distressing symptoms. Spontaneous pneumothorax complicating bronchial asthma is a rarer occurrence than subcutaneous emphysema and is a more serious one. Castex and Mazzei[38] reviewed the literature of twelve cases, with three deaths, giving a mortality of 25 per

cent. Engelhardt and Derbes,[39] in 1944, tabulated nineteen cases of pneumothorax complicating bronchial asthma. Death occurred in five of these. They added one of their own in which death resulted. The mortality rate was 25 per cent.

Many authors have suggested incisions in the suprasternal region for relief of emphysema in this area. Kirsner inserted a needle for the release of air in his patient. However, all the other cases, including the case presented, recovered with conservative treatment. It seems in these cases the alveolar tear tends to close spontaneously and rapidly. In the case reported, treatment with ephedrine, adrenalin or aminophylline failed to relieve the dyspnea or wheezing in the chest previous to the production of the subcutaneous emphysema when there was a marked alleviation of symptoms immediately. When this patient was in marked distress because of cyanosis and dyspnea, with respiration apparently fixed in a state of maximal inspiration, so much air was trapped in the tissues that it produced pressure on the blood vessels of the lungs, mediastinum and the heart. At that time the patient presented the characteristics of the malignant type of interstitial emphysema that the Macklins mentioned. However, with the escape of air into the neck, there was a sudden improvement in the clinical picture, and at this point the patient assumed the characteristics of the benign form with resultant recovery. The pressure gradient factor in asthma is probably produced by increased alveolar pressure and a decrease in the caliber of the pulmonary vessels due to the prolonged expiration. It is also possible, as Macklin and Macklin have already mentioned, that there may be, in addition, a congenital weakness of the alveolar walls or the presence of atelectasis. Kjaergaard[40] believed that rupture occurred in an emphysematous valve vesicle. With each inspiration more air entered the vesicle than left it, thus producing stretching and rupture. However, it is most important to minimize coughing, and the barbiturates would seem indicated. Fine, Hermanson, and Frehling[41] have shown that the nitrogen that is present in the tissues may be absorbed more rapidly by the use of oxygen in high concentration, that is, by increasing the diffusion pressure of nitrogen. The residual symptoms of asthma are not marked and usually last for a few days following the initial appearance of air in the tissues of the neck. At this stage injections of adrenalin afford relief for the asthmatic symptoms.

SUMMARY

1. A case of spontaneous mediastinal and subcutaneous emphysema complicating bronchial asthma is presented.

2. Twenty-five similar cases collected from the literature are analyzed.

I am indebted to Dr. L. L. Bell and Dr. W. Tierman for their interpretation of the evidence for air in the mediastinum shown by roentgenogram.

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MOLD ALLERGY*

I. Field Survey of Philadelphia Area

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A STUDY of the mold content of the air is one of the first requisites for a better understanding of the role molds play in causing hay fever and asthma. van Leeuwen[1-3] was the first to emphasize the importance of molds in allergic diseases of the climatic type. He believed that the type of soil, the type of construction, the sea level, and the proximity to large bodies of water influenced the type and the number of spores. He felt, therefore, that spores would be more abundant in low, moist localities.

Feinberg's work[4-8] in the United States, the first to contain a comprehensive field survey, stimulated many workers to investigate the mold problem in their particular locality. Feinberg's[5] survey showed a seasonal trend for *Alternaria* and *Hormodendrum;* the former began to increase in late June and subsided in mid-November, while the latter was increased from mid-June to mid-July and again from early August to early December. Other spores were present throughout the year but all were increased during warm weather. Feinberg's[6-8] studies led him to believe that the most important molds in the Chicago area were *Alternaria, Hormodendrum, Aspergillus, Chaetomium, Fusarium, Mucor, Rhizopus, Trichoderma, Cephalothecium, Actinomyces,* and yeasts.

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A partial survey (May 21 to September 21), done by Balyeat, Stemen, and Taft[9] in 1932, showed a fluctuation in the atmospheric spores from a high of 1,500 in June to a low of 200 in September. The only molds accounted for in this survey were either *Aspergillus* or *Penicillium*. Prince and Morrow[10, 11] conducted a survey of the mid-continental region of United States extending from the Great Lakes to the Gulf Coast. Semimonthly plate exposures were made at twenty-three stations over a two-year period. The mold counts from the Northern States showed a low winter and a high summer-to-fall incidence. Those from the South were highest in the winter, spring, and fall, diminishing in the late spring and summer. They correlated the high mold concentrations in the coastal area of Texas with north winds that came from the swampy interior of the state. The clinically important molds were *Monilia, Aspergillus, Penicillium, Trichoderma, Helminthosporium, Hormodendrum, Cladosporium,* and *Alternaria.*

Durham,[12-13] in an extensive study of the incidence of *Hormodendrum, Alternaria,* and rust spores in sixty-three localities throughout the United States found an increase in *Hormodendrum* spores from mid-May to the latter part of October, while the *Alternaria* spores began to increase in early June and persisted till mid-November. Smaller quantities of these spores could be found throughout the remainder of the year. The season of heavy atmospheric distribution was shorter in the North than in the South, although the peak months were the same (July, August, and September). The spore count was highest when strong winds came from the northwest, other things being equal. Rust spores also varied with the season and the locality, beginning about mid-June and lasting for several weeks. Smut spores first appeared on June 20 and reached their maximum concentration on July 6. Durham[14] also reported showers of *Alternaria* and *Hormodendrum* that originated in Minnesota and swept southward and eastward. In all these studies Durham stressed the fact that regional counts showed considerable variation and the question of mold concentration depended on the locality. Despite this variation there seemed to be a definite seasonal incidence, e.g., May to November. The method Durham utilized for these studies was the same as for his pollen studies, namely, the amount of spores deposited per twenty-four hours on 1.8 sq. cm. of a slide covered with petroleum jelly.

Schonwald[15] surveyed the western part of Washington by the plate method and found a prevalence of mold spores from October to February and again from late May through June. The most abundant molds were *Rhizopus, Penicillium expansium,* and *Trichoderma koningi,* in the order named. Pratt's[16, 17] survey of the New England region by the plate method showed an increased spore count during the spring months rising to a peak during July and August with a gradual diminution during the late fall. The seasonal increase was due almost entirely to *Alternaria* and *Hormodendrum.* The usual molds encountered were *Alternaria, Hormodendrum, Aspergillus, Penicillium,* and *Chaetomium.* Waldbott et al.[18] surveyed the air of southern Michigan from November, 1937, through November, 1938, and found that yeasts, *Penicillium,* and *Torula* were found perennially in appreciable quantities. *Alternaria,* while present throughout the year, showed a seasonal July to November increase. Other seasonal molds with low counts were *Hormodendrum,*

Macrosporium, Neurospora, Trichothecium, and *Trichoderma.* Stroh[19] in an incomplete survey of the Seattle area found a preponderance of *Hormodendrum* and *Alternaria* over all other species. Pennington[20] found a definite seasonal summer increase in *Alternaria, Hormodendrum, Acrothecium,* and *Spondylocladium* in the Nashville area from 1937 to 1939, inclusive. A recent mold survey by Alvarez and Quintero, from Havana, shows an increased mold count during the daytime, during periods of lowered barometric pressure, with high temperatures and with increased wind velocity. The direction of the wind altered the type but not the quantity of spores in the atmosphere. No mention is made regarding the seasonal variation in the quantity or the types of spores. The most frequent molds encountered in the order of their importance were *Hormodendrum, Mucor, Penicillium,* and *Alternaria.*

Thus, a review of the literature reveals that a major mold season exists in most localities in the United States. The season that is common to most areas begins in early May and persists till late October. The notable exceptions are the coastal area of Texas, where Prince and Morrow found an increase in mold spores during the winter months, and the western part of Washington, where Schonwald found an October to February peak in addition to the usual one in May and June.

The present study was undertaken in an attempt to establish the existence of a major mold season in the Philadelphia area. Since the flora of the Middle Atlantic States are so like those of the Philadelphia area, it was thought that the results of this survey might be applied to many adjacent areas. A common denominator was found among all the pollen surveys covering the Middle Atlantic States and it seemed feasible to expect the same thing of the molds. It was hoped that the knowledge uncovered by this survey would allow the clinician to correlate seasonal allergic symptoms with mold fluctuations and thereby arrive at an accurate etiological diagnosis in these cases.

PROCEDURE

It was obvious from the very beginning that no one method of counting spores could be regarded as satisfactory. The slide method, whereby one could count the number of spores deposited over 1.8 sq. cm. per twenty-four hours, had the advantage of counting individual, recognizable spores (*Alternaria, Hormodendrum, Helminthosporium, Fusarium, Acrothecium,* rusts, and smuts); however, one could neither identify nor count the smaller spores of the *Aspergillus, Penicillium, Mucor, Rhizopus,* or yeast groups. The plate method permitted one to count the number of colonies deposited on a petri dish over a certain period of time. Two drawbacks to this method were the inability to tell whether a colony arose from a single spore or a group of spores and the inability to grow certain molds, such as rusts. The plate method also had the added disadvantage of being exposed for a limited period each day so that the count might not be characteristic of either the quantity or types of spores when calculated on a twenty-four-hour basis. All estimations in this study will, therefore, refer to the number of colonies appearing on plate per ten-minute exposure. No attempt will be made to compare the slide counts with the plate counts for the reasons stated above. It was believed, however, that the use of both of these methods

would yield more information than either one, although neither could be used as a check on the other.

Slides covered with petroleum jelly were placed in a pollen shelter housed on the roof of a seven-story building located near the center of the Philadelphia metropolitan area and allowed to remain there for twenty-four hours. The time of this exposure was kept constant, e.g., from 12 o'clock noon of one day to 12 o'clock noon of the following day. The reason for choosing such a location for the pollen shelter was to avoid contamination by the molds from within the home itself that might not serve as a true indication of either the flora or the amount of atmospheric spores. These slides were collected daily, and 1.8 sq. cm. of each was counted. Since *Alternaria* assumed such a prominent place in the etiology of mold allergy, separate counts were made for it.

Standard petri dishes (3½ inches in diameter) containing a medium suggested by Henrici[22] for differential growth were exposed under the pollen shelter for ten-minute periods each day. This time interval was determined by exposing plates under the shelter for varying periods of time and choosing the one that yielded sufficient individual colonies without overgrowth. Longer periods of exposure yielded such luxuriant growth that it was impossible to either identify or count them. All plates were set out at approximately the same time (12 o'clock noon) each day so as to avoid variations attributable to the time of the day that the plates were exposed. Several times throughout the course of this study plates were exposed for ten-minute intervals each hour to note the variations in the atmospheric spore content at different times of the day. The colonies appearing on our plates were counted on the third and again on the fifth day after exposure. This latter count permitted the slower growing molds to reach maximum growth.

Previous observers, notably Prince[10] and Durham,[13] observed increased spore counts during north and northwest winds respectively. This phase of the problem seemed worthy of further consideration. The influence of the velocity of the wind and the amount of rainfall on the spore content of the air was also recorded. In cooperation with the U. S. Weather Bureau in Philadelphia we recorded the direction and the velocity of the wind as well as the amount of rainfall occurring during the plate and slide exposures. Correlation of these factors with the atmospheric spore content was then attempted.

RESULTS

Chart 1 depicts the total spore count as well as the *Alternaria* count during the month of June, 1939. The prevailing wind and its velocity is recorded and the presence of rainfall is indicated by an asterisk. One will note that peaks in the spore count occur regardless of the direction or the velocity of the wind. Theoretically, the velocity of the wind should increase the amount of spores deposited on a given area of a slide covered with petroleum jelly providing all other factors remain constant. The fact that increased velocity failed to yield higher spore counts merely indicates the variability of other factors influencing spore production and spore distribution. The direction of the wind should influence the atmospheric spore count only if it comes from, or passes

over, an area of increased spore production. Our inability to demonstrate a relationship between the direction of the wind and increased spore content of atmosphere may point toward the absence of any primary producing mold site in or about the Philadelphia area. This seems more likely when one examines the territory adjacent to Philadelphia and finds an absence of swamps and stagnant streams. Rainfall, on the

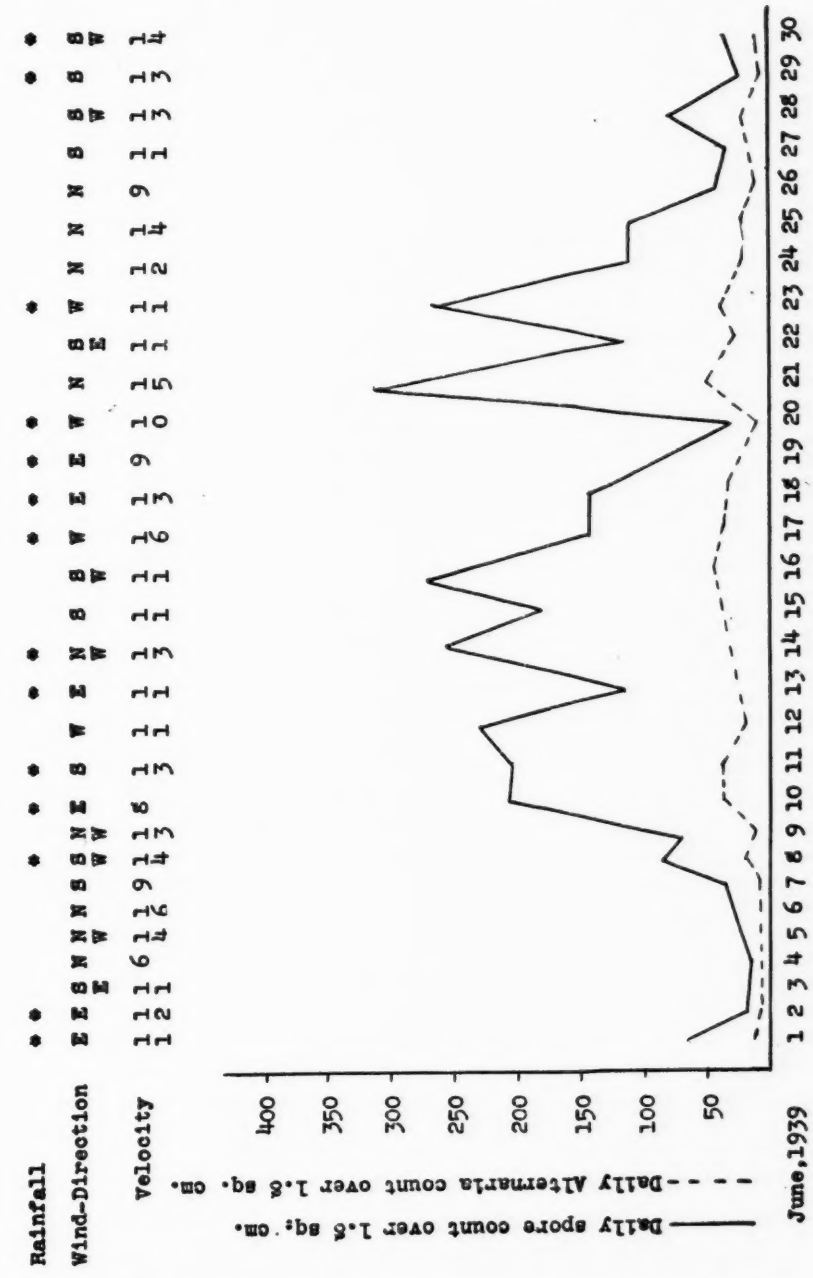

Chart 1.—Daily spore count (slide method).

other hand, seemed to decrease the amount of mold spores deposited on our slides. This was best demonstrated by exposing petri dishes before and after a rainstorm. A definite decrease in the number of colonies produced on the exposed plate was obtained following such a rainfall. The plate counts for June, 1939 (Chart 2) corroborated the above find-

ings regarding the effect of velocity and direction of wind on the spore content of the air. Since none of the exposures were made during a rainstorm, its influence on the plate counts was not determined.

The question arises, whether or not the quantity of spores in the atmosphere vary with the time of day. Our observations lead us to believe that there is a direct relationship. Plates exposed at different times

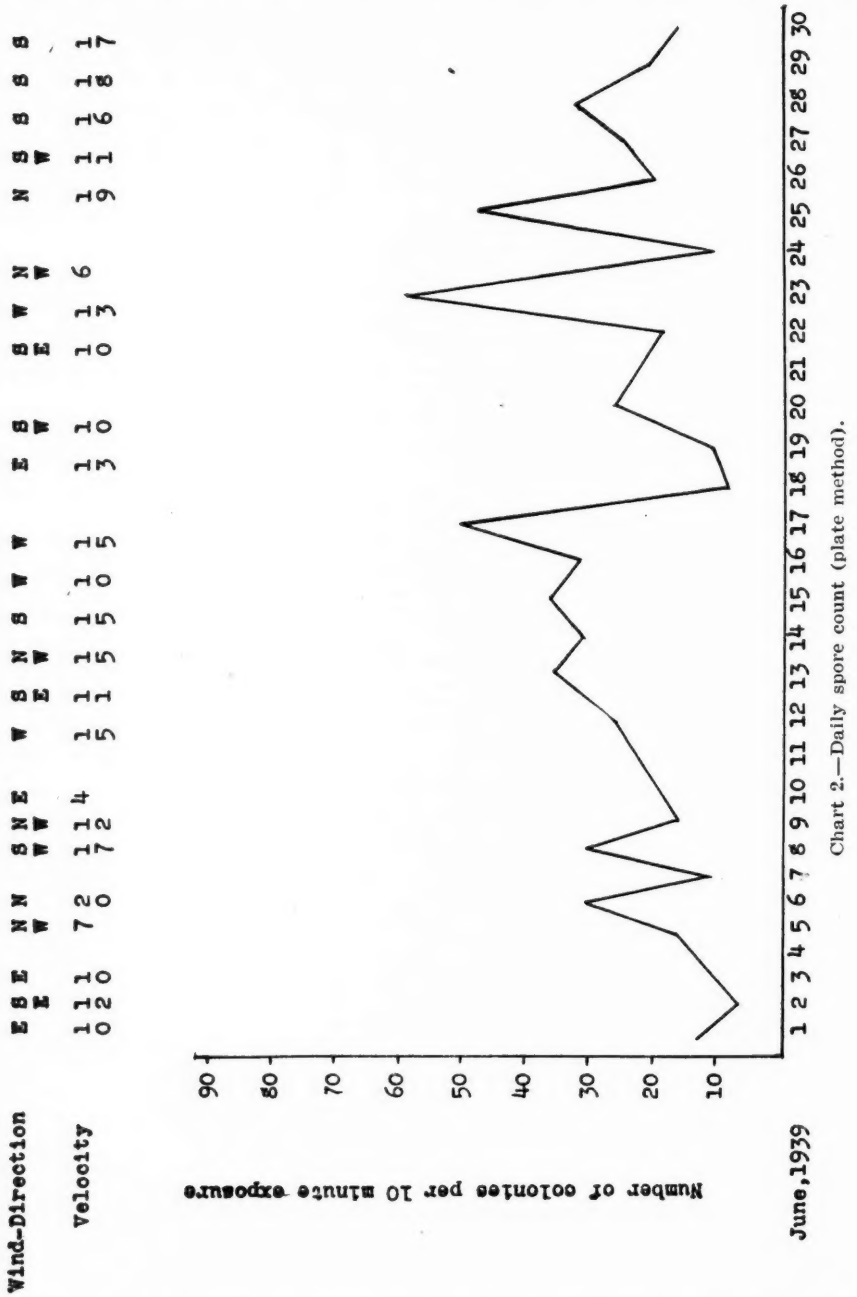

Chart 2.—Daily spore count (plate method).

of the day show varying amounts of mold colonies; the period of maximum production is in the early afternoon. Chart 3 shows two rather characteristic graphs of this variation. Of particular interest are the low morning and late afternoon counts as compared with the relatively high ones of the early afternoon.

Another question concerns seasonal variation in the mold spore content of the air. One must approach the answer to this query with caution, for mold spores are present in varying quantities in the atmosphere throughout the year. The time of greatest mold production and dissemination occurs during the months of April to October when

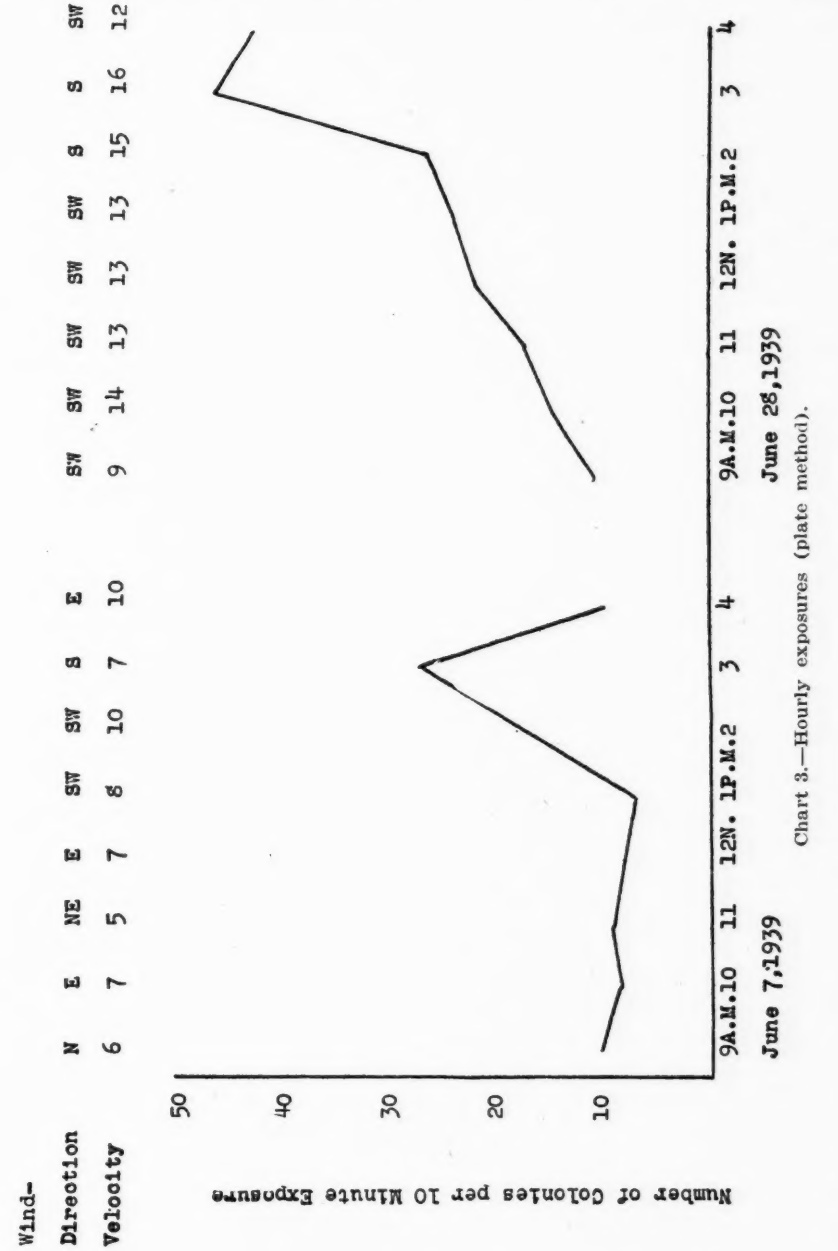
Number of Colonies per 10 Minute Exposure
50
40
30
20
10
Wind-
Direction
Velocity
N E NE E SW SW S E SW SW SW SW SW S S SW
6 7 5 7 8 10 7 10 9 14 13 13 13 15 16 12
9A.M.10 11 12N. 1P.M.2 3 4
June 7,1939
9A.M.10 11 12N. 1P.M.2 3 4
June 28,1939

Chart 3.—Hourly exposures (plate method).

warmth and moisture, necessary for luxuriant mold growth, are usually present. In analyzing the results of this study it will be necessary to divide the findings into two categories because of the marked variations obtained with each method of estimation, namely, the gravity slide method and the plate method.

Two hundred seventy plate exposures were made from June 1, 1939, to May 31, 1940. The results of these observations may be seen on Chart

4. It will be noted that mold spores are present throughout the year in appreciable quantities, being highest during spring and summer months and lowest during the winter months. During the time of highest colony production the only molds that were consistently observed on exposed plates were *Alternaria, Hormodendrum,* and the yeasts. The other mold colonies found sporadically throughout the period of observation included *Aspergillus, Penicillium, Mucor, Monilia, Helminthosporium, Chaetomium, Fusarium,* and *Rhizoctonia. Helminthosporium* and *Fusarium* were encountered more frequently during the months of June to October. A similar survey was made during the months of May to November, 1941, with essentially the same findings. One could,

	JUNE 1939	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	JAN. 1940	FEB.	MARCH	APRIL	MAY
1	12	71	50				5			18	67	134
2	6		36				2	0	4	18	8	11
3	10	11	9			27		0	19		26	15
4			17			29	4	0		4	11	18
5	15	30		19	1		0		9	32	50	
6	30	12		5	2	21		6	6	147	52	30
7	9	29	7		59	5	25		7	31		47
8	30		10	1		20	34	3	29	12	41	14
9	15		4	0	30	10	7	0	27		45	29
10	20	22			0	28		0	13		24	11
11		18	0	1	81	15	14	0		70	76	22
12	27	20	0	5	10		5	0	36	21	20	
13	34	30		1	13	34	0	0	8	13	21	28
14	31	20	0	2	0	8	2		8	6		15
15	37	2	0	0		8	2	0	11	6	18	52
16	30		9	0	0	28	9	0	4	6	12	2
17	50	20		0	0	16		0	3		36	50
18	8		2	3	2	17	0	0		23	5	
19	10	0	23		0		0	8	5	36	3	32
20	25	20			0	21	1	23	4	6	5	
21		37	0		0	2	2	0	7	5		34
22	17	37	0		0	4		0	24	27	70	7
23	58		0		0		4	26	39		18	51
24	9	47	0			3			37		36	23
25	45	26	3	19	19	4					8	31
26	21	7		4	4		0		56	46	30	48
27		34			0	2	4		11	44	30	48
28	31			2	2	2	0		3	19		78
29	21	26		11	11	3	1		13	7	24	
30	13			5	4	0	1			9		
31		44										26

Chart 4.—Daily records of mold colonies per ten-minute exposure.

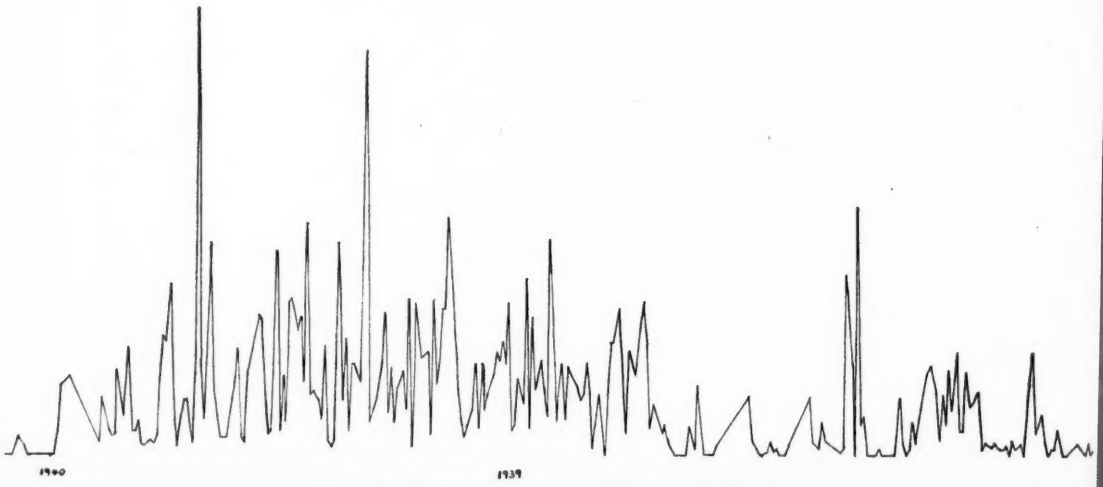

Chart 5.—Daily spore count (plate method).

	JUNE 1939	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	JAN. 1940	FEB.	MARCH	APRIL	MAY
1	7		83	67	24		0		0	1	0	2
2	1		59		8	4	4	0	0	0		1
3	7	53	70		0	2	↓	1	0	↓	4	1
4	↓	↓			5	7	0	1	↓	0	2	2
5		139	61	36	7	↓	↓	0	0	0	2	↓
6		42	↓	18	19	3			0	0	1	7
7	4	43	35	18	19	7	6	0	1	0	↓	
8	15		4	93	↓	9	1		1		0	
9	9		58	62	76	3	7	0	0	0	2	7
10	79	78		↓	24	5	↓	0	1	↓	0	0
11	↓	19	15	14	52	12	0	0	↓	0	2	1
12	13			6	29	↓	1	0	0	0	↓	↓
13	15	39		5	47	2	1	0	2	1	↓	6
14	18		10	7	150	7	1	0	0	3		3
15	40	13	9	14	↓	1	1		0	0	1	3
16	48	↓	56	95	6	9	1	1	0	1	0	1
17	83	17		↓	38	0	↓	0	0	↓	0	1
18	↓	26		17	2	7	2	2	↓	0	1	5
19		4	20	1	39	↓	0	1	0	0	1	↓
20	3	10	↓	29	7	2		0	0	0	↓	4
21	51	5	21	15	80	7	0	0	1	0	0	3
22	20	21	46		↓	4	1		0	0	1	5
23	38	↓	35	75	34		3	1	0	0	0	4
24	34	41	50	↓	1	0	↓	0	0	↓	1	0
25	↓	35	16	49	4	1		0	↓		0	1
26	13	40	51	60	7	↓	1	0	1	0	0	↓
27	16	1	↓	5	28		1	0	0	0	2	5
28	19	16	35	11	41	3	1	0	0	0	0	
29	7	69	44	29	↓	0	0		1	0	1	
30	8	↓	11	24	7	0	0	0				
31		105	1		5		↓	0				

Chart 6.—Daily *Alternaria* counts over 1.8 square centimeters.

	JUNE 1939	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	JAN. 1940	FEB.	MARCH	APRIL	MAY
1	69		306	183	91		56		5	4	4	11
2	7		294		27	18	30	3	11	5		3
3	29	157	175		36	21	↓	4	13	↓	7	5
4	↓	↓			12	27	21	10	↓	3	6	11
5		1003	288	130	68	↓	↓	13	4	7	7	↓
6		104	↓	69	142	18			4	1	8	10
7	34	118	204	43	142	40	44	15	4	3	↓	
8	87		19	265	↓	65	10		11		3	
9	74		135	139	255	24	51	7	5	13	57	13
10	411	218		↓	189	66	↓	2	18	↓	10	6
11	↓	75	76	50	105	35	17	3	↓	1	13	9
12	231			41	73	↓	14	4	10	0	↓	↓
13	115	327		20	108	24	14	3	6	2		12
14	259		52	23	328	21	1	4	6	6		46
15	177	146	19	34	↓	18	4		9	11	9	14
16	269	↓	89	207	74	34	11	7	6	11	2	10
17	282	37		↓	63	14	↓	7	3	↓	10	10
18	↓	65		17	7	17	9	7	↓	3	7	13
19		74	26	6	95	↓	4	10	2	1	2	↓
20	18	45	↓	7	94	9		2	6	1	↓	56
21	315	23	37	114	222	12	5	10	2	2	6	8
22	113	67	138		↓	9	6		4	1	4	34
23	263	↓	103	244	87		9	11	7	0	7	13
24	223	191	85	↓	14	0	↓	4	15	↓	5	14
25	↓	131	57	140	19	4		9	↓		1	49
26	42	80	331	208	33	↓	5	1	5	1	6	↓
27	33	11	↓	32	69		6	4	9	2	6	25
28	73	20	103	51	94	14	3	5	3	2	0	
29	19	128	109	174	↓	3	4		6	4	3	
30	30	↓	50	91	23	32	3	5				
31		249	5		43		↓	5				

Chart 7.—Daily total mold count over 1.8 square centimeters.

therefore, venture the opinion that the only molds in this group that might be held responsible for seasonal allergies in the Philadelphia area would be *Alternaria, Hormodendrum, Helminthosporium, Fusarium,* and the yeasts.

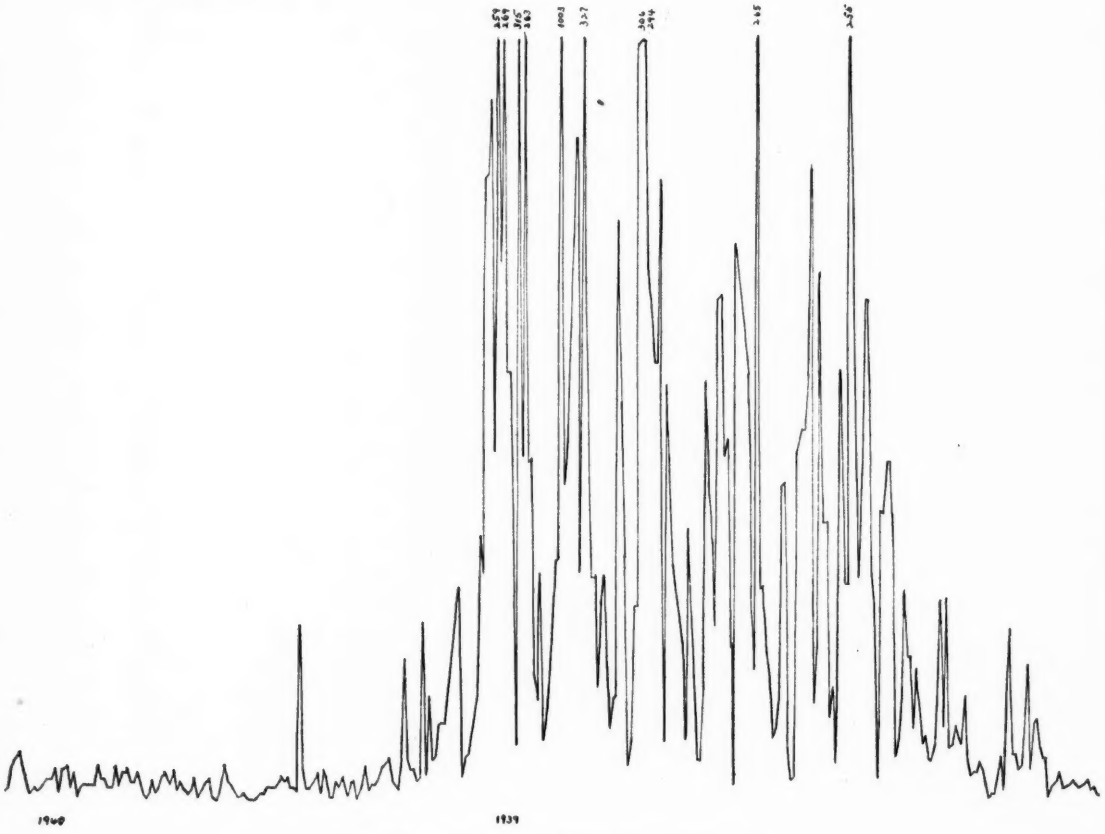

Chart 8.—Daily spore count (slide method).

Contrasted to this phase of the survey are the results of two hundred seventy-eight slide exposures depicted in Charts 6 and 7. The former shows the results of the *Alternaria* count and the latter the total spore counts covered by this survey. The arrows on the charts indicate that the slides were exposed for more than a single day, usually over week ends and holidays, and therefore represent a forty-eight- or seventy-two-hour count. When these figures are arranged graphically (Chart 8) we see a distinct seasonal tendency among the group of molds possessing relatively large and distinctive spores. Their season seems to begin about the middle of May, rapidly approaching its peak sometime in June with continual high counts until the middle of October. The *Alternaria* count always seems to parallel and form an appreciable part of the total count. Spores of this series may be seen in slides throughout the year but never in the same quantity as during the mid-May to mid-October period. The mold spores responsible for this increased seasonal count were *Alternaria, Hormodendrum,* smuts, rusts, *Helminthosporium,* and *Fusarium,* their relative degree of importance being in the order named. Reference to Charts 7 and 8 will corroborate the observations of Durham relative to the occurrence of mold showers during

the fall months and will explain some of the rather high counts obtained during that period.

DISCUSSION

The wide variation in the results of the plate method of counting molds as contrasted with the gravity slide method emphasizes the necessity for using both procedures in determining the mold flora of a given locality. Each method of study has its own particular advantages and disadvantages, and correlation between the two is not feasible for reasons already explained. There exists, however, general agreement between the two methods of study in that both showed elevations during the spring and summer months when the elements of warmth and moisture, conducive to rapid mold growth, were present. Other than this, no direct relationship was found between the direction and velocity of the wind and the number of mold spores present in the air. As previously suggested, this merely indicates the lack of swamp or other mold-producing areas in this locality.

It may be significant that the seasonal increase in molds was due primarily to those molds possessing the larger spores. There was also a minor increase in molds with smaller spores. If, as has been reported by other investigators,[4-11] the molds possessing large spores and a seasonal period of distribution are responsible for the production of most cases of seasonal mold allergy, then one might explain this phenomenon by assuming that these spores contain a relatively strong antigen.

SUMMARY

1. The presence of a major mold season beginning in mid-May and lasting till mid-October has been demonstrated. This was shown best by the use of the gravity slide method, although the same results may be obtained with the plate method by careful examination of the types of colonies obtained during that period.

2. There was a disproportionate increase in those molds possessing large spores during this season, most important of which were *Alternaria, Hormodendrum,* and smuts.

3. No direct correlation could be established between meteorologic conditions and the amount of molds present in the atmosphere.

4. There seemed to be an hourly variation in the spore content of the air.

5. No one method of estimating the mold content of the atmosphere was found satisfactory, and it is suggested that future surveys utilize both methods.

6. Spore showers were observed frequently throughout this study.

We wish to thank Dr. Samuel Feinberg of Chicago for his generosity in supplying us with mold cultures and with information that made this study possible. For aid in identifying many of the molds found on our plates, thanks are given to Dr. Franklin D. Benedict, of the Botany Department of Temple University, and to Dr. Harlan H. York, of the Botany Department of the University of Pennsylvania.

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1614 LOCUST STREET.

RELIEF OF DERMOGRAPHISM AND OTHER URTICARIAS OF HISTAMINE ORIGIN BY A SYNTHETIC BENZHYDRYL ALKAMINE ETHER*

SAMUEL M. FEINBERG, M.D., AND SIDNEY FRIEDLAENDER, M.D., CHICAGO, ILL.

THE whealing of urticaria factitia or that produced by a single stroke of the skin in dermographism was shown many years ago by Lewis[1] to constitute an exaggerated physiologic response. When the physical stimulus is repeated sufficiently or is intense enough, the skin of all young subjects responds by whealing. Lewis and Grant[2] showed further that the wheal produced by stroking in dermographism is in all respects identical to the wheal produced by histamine in nondermographic subjects. Some experiments with the wheal fluid on the skin of normal subjects and on the guinea pig uterus indicated an activity resembling histamine. In later experiments, Lewis and Harmer[3] demonstrated a general rise in skin temperature and flushing of the face following the

*From the Division of Allergy, Department of Medicine, Northwestern University Medical School.

extensive stroking of the skin of the trunk of subjects with urticaria factitia. They concluded that the effects were indistinguishable from those due to histamine injection. No such effects were noted in subjects with normal skins.

Histamine antagonists of various types have been proposed from time to time.[4] These substances differ in their mechanism of action, but, in general, they have been found to be either insufficiently effective or too toxic when administered in amounts sufficient to counteract the histamine action. However, a new synthetic chemical, β-dimethylaminoethyl benzhydryl ether hydrochloride, was demonstrated by Loew and his associates[5] as an efficient histamine antagonist of low toxicity. Fatal bronchoconstriction in guinea pigs following the inhalation of histamine by special method was prevented by prior administration of this drug. The symptoms of anaphylactic shock and the mortality rate from intravenous histamine were also reduced. The intraperitoneal dose of this chemical was 1/30 to 1/60 of LD-50. The LD-0 intravenous doses in rabbits were 7.5 mg. and in dogs 25.0 mg. per kilogram.

The relief obtained in a case of cold urticaria in a clinic patient was called to our attention by Dr. T. G. Randolph of our department. Shortly thereafter another case of cold urticaria in our private practice was likewise kept under control by the use of this drug. These experiences encouraged us to try the use of this benzhydryl alkamine ether in two women with severe urticaria factitia of several years' standing. The results were dramatic, relief from the whealing and itching occurring after the first dose. In these and a third later case of urticaria factitia in a little girl, the drug was stopped and started on numerous occasions, and always with the same results. Relief was obtained on administering the drug and a recurrence of symptoms followed in six to twenty-four hours after discontinuing it. While we prescribed doses of 50 to 100 mg. three times daily it was possible for the patient to learn to adjust his dose and interval to his own requirements.

Our experience with urticaria factitia led us to investigate the effect of this drug on cases of dermographism which we encounter in our practice as an obstacle to the performance of skin tests. An appreciable number of our patients on whom we wish to make skin tests present the handicap of dermographic whealing which creates difficulties in the interpretation of the reaction. This phenomenon does not appear to be more common in allergic than in nonallergic subjects. The usual steps in circumventing this difficulty are the use of the intracutaneous technique or passive transfer.[6] The objections to these procedures are several and are discussed elsewhere.[6] We, therefore, began to use this drug* in our dermographic patients, instructing them to take the medication for several days prior to their appointment for skin tests. Subsequently, we found that from 50 to 150 mg. of this drug taken over a period of a few hours prior to skin testing was equally efficacious.

We have used this antihistamine substance in thirty patients who demonstrated dermographism, in the performance of scratch tests. Usually, we direct the patient to take 50 mg. of the drug five hours, three hours, and one hour before the tests are to be made. In exceptional instances, slightly larger doses have had to be employed. The dermographic patients comprised twenty adults and ten children. The atopic manifestations for which they consulted us included asthma, seasonal and nonseasonal rhinitis, urticaria, and atopic dermatitis. In eighteeen of these patients positive atopic skin reactions were demonstrated after the dermographism was controlled. The allergens reacting in-

*The drug was supplied by the Research Department of Parke, Davis & Company, Detroit, Mich.

cluded pollens, fungi, house dust, animal danders, and some foods. For practical purposes, at least, the use of this drug did not interfere with the production of the specific skin reaction to the antigen. In all of the patients treated in this manner there was either complete or partial inhibition of the dermographic whealing. This effect was obtained consistently on each of a number of visits by most of the patients. When the drug was omitted the dermographism returned. About the only untoward effect of this drug we noted was a feeling of sleepiness and lassitude occurring in some of the patients.

The relief obtained in cold urticaria prompted us to try this drug in several cases of rhinitis and asthma in which there was a history that temperature change would precipitate or aggravate the manifestation. In none was there benefit obtained. Since Lewis and Grant[7] suggested that the allergic reaction acts on the tissues by the liberation of histamine-like substances, and since Loew and Kaiser[8] found this benzhydryl alkamine ether markedly effective in alleviating shock in guinea pigs, its action in a few instances of atopic conditions was tried. At this time we are not presenting a complete study of this phase of the subject, but we merely wish to mention that the behavior of this drug in such cases was, in general, unlike that in cold urticaria and dermographism. In none of twelve cases of allergic rhinitis and seventeen cases of asthma was there any improvement. Two patients with chronic urticaria were almost completely controlled when taking this drug, while two others obtained no relief. In four cases of acute urticaria it was not possible to evaluate the effectiveness of this remedy. The itching was alleviated in one case of atopic dermatitis, one case of contact dermatitis, and one case of pruritus of unknown cause.

Further studies on the action of this drug, with respect to its behavior on the histamine and antigen-antibody reaction, and possible mode of action, will be presented later.

SUMMARY

The new histamine antagonist, β-dimethylaminoethyl benzhydryl ether hydrochloride, is an effective palliative remedy in dermographism and is particularly useful in the type of dermographism interfering with cutaneous testing for atopic manifestations.

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ADDENDUM

Since the above was written, we have obtained relief with this drug in several cases of acute and chronic urticaria, in one case of serum sickness, in two cases of chronic rhinitis, and in several cases of itching in atopic dermatitis.

CONTACT DERMATITIS DUE TO CONTACT WITH CHROME 17 PER CENT STEEL IDENTIFICATION TAGS OF THE UNITED STATES NAVY

M. Coleman Harris, M.D., Beverly Hills, Calif.

WITHIN recent years, considerable interest has been centered around contact dermatitis with particular reference to its importance in industrial and factory workers. Opportunities to observe dermatological reactions to unusual substances were amply afforded in the United States Naval Service. The number of materials causing reactions were sundry and diverse, of animal, vegetable, and mineral origin. One of the more interesting cases of contact dermatitis resulted from contact with 17 per cent chrome steel with which the identification tags of the Navy are made.

Chrome compounds producing dermatitis have been reported frequently in medical literature. The toxic and powerfully irritant qualities of the trioxide of chrome or chromic acid and the alkaline chromates are well known. However, chromium in its metallic state is considered nontoxic and, because of its hardness, durability, and high melting point, is used in the manufacture of the metal identification tags of the United States Navy.

Because of the manner in which these tags are worn, namely, next to the skin and in close contact with it, it is reasonable to assume that were chrome steel a common cause of contact dermatitis many cases would have been reported. Apparently this has not been the case, for careful inquiry among Naval medical officers and careful search of Naval medical literature reveal that no cases of contact dermatitis due to such cause have been reported.

The subject in the case herewith reported is O. T., Stewards Mate, third class, a Negro, 27 years of age. His mother and father are living and well. One brother and one sister are living and well. No history of asthma, hay fever, migraine, eczema, or other manifestation of allergy was obtained in the family history, other than that his brother had experienced several attacks of urticaria the cause of which was unknown. The patient admitted that he also had suffered from urticaria due, in his opinion, to the ingestion of grapefruit or lemons. He had never been studied or tested out but had observed that whenever he ate either grapefruit or lemon he broke out in hives. No other food caused similar reaction. O. T. had always worked in the fields. He was never employed in a factory. The only illness for which he consulted a physician prior to entering the Navy was a fever, in 1923. This was diagnosed as dengue fever. Physical examination was negative with no abnormal signs other than an excessively oily skin and pes planus, 2 degrees. He perspired freely.

On entering the United States Navy, O. T. was given two identification tags and, in accordance with Naval regulations, was instructed to wear them at all times. (The identification tag is shown on the right wrist in Fig. 1.) It is the familiar regulation identification tag of the United States Navy and is composed of 17 per cent chrome steel. After the tag had been in contact with the skin for forty-eight hours, O. T. complained of an itching and burning sensation which became intensified the following day, with the appearance of marked erythema and vesicles. Contact of the skin with the Navy chrome

steel identification tag for a period of seven days resulted in a marked erythematous patch, not clearly defined, papular, with marked vesiculation; there was some oozing. The lesion was pruritic and the erythema extended beyond the borders of the lesion (Fig. 2; also, left wrist, Fig. 1). The itching and discomfort were so great the location of the tags was changed from the wrists to the ankles.

Fig. 1.—Official photograph, U. S. Navy.

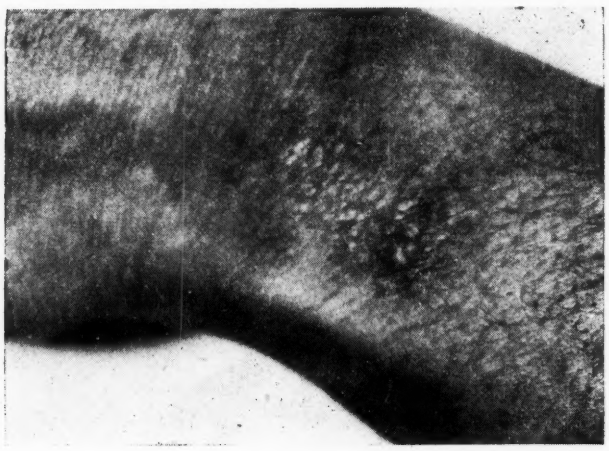

Fig. 2.—Official photograph, U. S. Navy.

The marked sensitivity of this patient to chromate salt was demonstrated by the rapidity and markedness of the reaction. The same condition arose when the tag was worn around the neck. The lesions resulted after contact for two weeks and lasted over eighteen months, thus demonstrating the common tendency of the lesion to exist long after contact has been removed.

Fig. 3 shows a lesion, resembling a destructive burn, caused by two weeks contact of skin with the metal twelve months previously.

Wearing the tag outside a cotton skivy undershirt or covering it with muslin did not protect the skin of the neck. As long as perspiration seeped through, the

lesion appeared. The only substance that appeared to render protection was a leather pouch, impermeable to sweat.

It should be noted that generalized symptoms of chrome poisoning were never observed in this patient. At no time were cramps, spasms, twitchings, visual disturbances, fever, or gastric or urinary symptoms complained of. All laboratory tests were negative. Repeated urine examinations were normal. Blood Kahn was negative. Blood counts disclosed no leucocytosis and but 3 per cent eosinophiles.

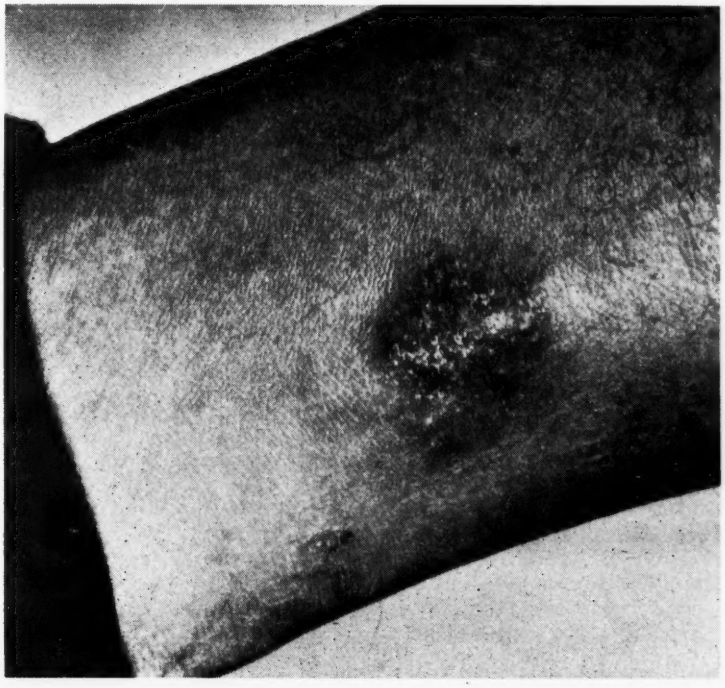

Fig. 3.—Official photograph, U. S. Navy.

Material was not available aboard ship for patch testing with a bichromate solution. Excessive sweating resulting in a greater solubility of the chromates, may have been a factor in this marked sensitivity.

SUMMARY

1. A case of presumed allergic skin reaction to the chrome 17 per cent steel identification tag of the United States Navy is herewith reported.

2. It is assumed that dermatological reactions to these tags have been extremely rare since, to the author's knowledge, none have been reported in Naval medical literature.

Editorial

Allergy to Penicillin

SINCE penicillin is rapidly becoming one of the most widely administered therapeutic substances, it is well that we ponder over its possibilities as a cause of allergic reactions. Thus far, several reports dealing with allergic effects from penicillin show reactions which may be classified into several types. One common allergic response consists of urticaria or angioneurotic edema. Keefer and his associates[1] found fourteen such instances in five hundred cases of penicillin therapy. In some of the patients the urticaria did not appear for several days after the administration of the drug. Lyons[2] reported that 5.7 per cent of his cases experienced urticarial reactions. The urticaria occurred after the first or after subsequent treatments. He emphasizes the fact that the penicillin therapy may be continued and mentions that the cutaneous and ophthalmic tests are negative in these cases before and after the urticaria. He regards this as an "atypical sensitization phenomenon." Criep[3] made a more extended study on a case of urticaria from penicillin. The attacks began to occur only after a number of injections of the drug, but recurred on subsequent reinjection. Intradermal tests with 1:100 penicillin were positive, while the culture media gave negative tests. Criep also found reagins. Direct skin tests with Penicillium extract (dilution and technique not stated) were negative. The majority of workers regard most of the urticarial reactions as of the serum sickness type of hypersensitiveness. The case reported by Criep is apparently akin to the reactions previously reported to insulin and liver extract.

A second type of allergic response has been an eruption, either vesicular, bullous, or papular, and generally followed by desquamation. Graves and his associates[4] described two cases in which vesicular lesions developed within twenty-four hours after the first injection of penicillin. Repetition of the injections aggravated the dermatosis. Both patients had given histories of dyshidrosis and positive reactions to trichophytin. In Case 1, a patch test was negative, while an intradermal test (with 0.1 c.c. containing 500 units) was positive at the end of ninety-six hours. Scratch tests performed with many other antigens, including fungi, were negative. The second case gave a negative intradermal test with penicillin. Cohen and Pfaff[5] mention a case of acute generalized erythematovesicular eruption with fever and toxic symptoms. Binkley and Brockmole[6] describe a reaction consisting of a papular eruption, itching, and desquamation. This patient also had a dermatophytosis. Patch and conjunctival tests with penicillin were negative. A case of bullous dermatitis occurring four days after penicillin injection is reported by Morris and Downing.[7] No skin tests or other specific tests were made. There appears to be a general feeling that the vesicular type of allergic response is in some way connected with the presence of fungus infection of the skin.

A third type of penicillin allergy is contact dermatitis. Pyle and Rattner[8] reported dermatitis on the face and genitalia in a physician who prepared and administered penicillin. Patch tests with the commercial and crystalline penicillin were positive, while the culture medium gave negative reactions. Silvers[9]

described a similar case in a chemist, but, in this case, the patch tests reacted with the commercial preparation but not with the crystalline penicillin. Similar instances are reported by Hanson[10] and Nelson and Sandt.[11] In the latter cases, patch tests with the commercial penicillin were positive, but no tests were made with the crystalline drug. In a case of dermatitis described by Binkley and Brockmole[6] both a positive patch test and delayed positive intradermal (strength of solution not stated) reaction were obtained. It is of interest to note that, while the patch test with a penicillin solution was positive in a case of dermatitis reported by Barker,[12] the autoclaved solution failed to produce a reaction. In 524 patients tested for sensitivity to penicillin ointment by Cohen and Pfaff,[5] five had positive reactions to the patch test.

Another potential type of penicillin hypersensitiveness is suggested by the finding of Rostenberg[13] that repeated intradermal injections of penicillin at five-day intervals caused the Arthus type of response in the majority of subjects. Welch and Rostenberg[14] also describe a tuberculin type of response to penicillin. A person who had had previous contact with molds, but not with penicillin, showed a tuberculin type of reaction to commercial and crystalline penicillin. The patch test was positive only on the previously injected area. No reagins were found. The authors did not make any tests with the media or the mold. The authors, in a note added to their paper, state that subsequently they found that, in testing 140 persons unexposed to molds, about 5 per cent were found to show a tuberculin type of reaction to the initial injection of crystalline penicillin.

Much needed light on the sensitizing properties of penicillin should come from anaphylactic experiments. McClosky and Smith[15] found that anaphylactic sensitization could be obtained in guinea pigs with commercial penicillin. The results were not uniform, however. Much more instructive information would have been furnished if the experiments had included cross reactions with crystalline penicillin, media, and the intermediary products of penicillin manufacture.

Almost all of the reports mentioned lack, in one respect or another, the essential details to provide a complete picture of the source and mechanism of penicillin allergy. The source of the allergen has not been satisfactorily determined. Presumably, it may arise from its presence in the Penicillium fungus, in the media, in the chemicals added in the preparation of penicillin, in the interaction between the chemicals and intermediary products, and in the penicillin itself. No concerted attempt has been made to localize the source of this allergen. That penicillin contains very little, if any, of the antigen residing in the Penicillium fungus which is ordinarily responsible for clinical mold asthma and rhinitis, has been demonstrated by Feinberg.[16] No doubt, more than one antigen is involved in the various types of allergic reactions. More complete immunologic investigation of the allergic patients and more extensive animal experimentation are needed to solve the problem of the origin and mechanism of allergy to penicillin.

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3. Criep, L. H.: Allergy to Penicillin, J. A. M. A. **126**: 429, 1944.
4. Graves, W. N., Carpenter, C. C., and Unangst, R. W.: Recurrent Vesicular Eruptions Appearing During Administration of Penicillin, Arch. Dermat. & Syph. **50**: 6, 1944.
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7. Morris, G. E., and Downing, J. G.: Bullous Dermatitis (Dermatitis Medicamentosa) From Penicillin, J. A. M. A. **127**: 711, 1945.
8. Pyle, H. D., and Rattner, H.: Contact Dermatitis From Penicillin, J. A. M. A. **125**: 903, 1944.
9. Silvers, S. H.: Contact Dermatitis From Amorphous Sodium Penicillin, Arch. Dermat. & Syph. **50**: 328, 1944.
10. Hanson, P. S.: Contact Dermatitis Caused by Commercial Penicillin. A Case Report, M. Bull. North African Theat. Op. **2**: 118, 1944.
11. Nelson, L. M., and Sandt, K. E.: Contact Dermatitis of Eyelids as Result of Penicillin, M. Bull. North African Theat. Op. **2**: 62, 1944.
12. Barker, A. N.: Allergic Reactions to Penicillin, Lancet **1**: 177, 1945.
13. Rostenberg, A., Jr.: Local Penicillin Therapy, Arch. Dermat. & Syph. **50**: 330, 1944.
14. Welch, H., and Rostenberg, A., Jr.: Hypersensitivity of Tuberculin Type to Crystalline Penicillin Sodium, J. A. M. A. **126**: 10, 1944.
15. McClosky, W. T., and Smith, M. I.: Experiments on the Sensitizing Properties of Penicillin, Proc. Soc. Exper. Biol. & Med. **57**: 270, 1944.
16. Feinberg, S. M.: Penicillin Allergy. On Probability of Allergic Reactions in Fungus-Sensitive Individuals; Preliminary Experiments, J. ALLERGY **15**: 271, 1944.

S. M. F.

American Academy of Allergy

NEWS AND NOTES

ANNUAL MEETING, PALMER HOUSE, CHICAGO, ILL.

DEC. 10 AND 11, 1945

HOTEL RESERVATIONS

It is imperative that hotel reservations be made as quickly as possible.

The Palmer House has assigned 150 double rooms for our members. This will not be sufficient for all visitors and those who do not obtain reservations should try other hotels. If you can possibly arrange to take a double room with a friend, the facilities will be considerably increased. Be sure to write for reservations early.

In order to assist you in planning your time of arrival in Chicago, the following tentative outline of the schedule of events may be of help:

Sunday afternoon and evening, December 9—Open house, cocktails, Chicago members of American Academy of Allergy hosts

Monday, December 10—Scientific meeting

Monday evening—Cocktail party and banquet

Tuesday, December 11—Scientific meeting

Tuesday afternoon—Business meeting

The details of the above events and arrangements for them will be communicated to you at a later date.

The following additional hotels are suggested:

Downtown hotels

Stevens Hotel	720 S. Michigan Ave.
Blackstone Hotel	S. Michigan Ave. at Balbo
Sherman Hotel	106 W. Randolph St.
Bismarck Hotel	171 W. Randolph St.
Morrison Hotel	79 W. Madison St.
Chicagoan Hotel	67 W. Madison St.

North (near downtown)

Drake Hotel	Walton Pl. and Michigan Ave.
Knickerbocker Hotel	163 E. Walton Pl.
Continental Hotel	505 N. Michigan Ave.
St. Clair Hotel	162 E. Ohio St.
Seneca Hotel	200 E. Chestnut St.

Committee on Arrangements,

S. M. FEINBERG, M.D., Chairman
185 N. Wabash Avenue
Chicago 1, Ill.

PROGRAM

Monday, December 10

9:00 A.M.

Histamine Azoprotein in the Treatment of Allergy, M. J. Cohen and Harold J. Friedman

Clinical and Serological Study of Histamine Azoprotein in Cases of Ragweed Hay Fever, Selian Hebald, Robert A. Cooke, and Lillian Downing

Clinical Evaluation of Histamine Azoprotein, Harold D. Dundy, Benjamin Zohn, and Robert Chobot

Chemical Investigation of Giant Ragweed Pollen, Gilbert C. H. Stone and Joseph Harkavy

Studies on the Immunological, Physical and Chemical Nature of Pollen "Fractions," Mary H. Loveless and Arden Moyer

Leucocyte Fragility in Transitory Leucopenia, T. L. Squier

Variations of Blood Eosinophiles and Total Leucocytes Following Test Feeding of Foods, T. G. Randolph and F. A. Rawling

Influence of Soy Bean Products on the Plasma Lipids and the Course of Eczema, Albert V. Stoesser

12:30 P.M. Luncheon

2:00 P.M.

Guest speaker, Dr. J. M. Robison, Houston, Texas (Subject to be announced)

Symposium on Infectious Asthma

Bacterial Allergy—Henry Scherp

Recognition, Leslie Gay

Medical Management, Alvan L. Barach

Surgical Management, F. D. Woodward

4:00 to 5:00 P.M.

Questions and answers on Infectious Asthma

Questions from audience

Answers by speakers and W. C. Spain and Harry L. Alexander

6:15 P.M. Cocktails

7:15 P.M. Annual Dinner

Tuesday, December 11

9:00 A.M.

Use of Oral Penicillin in Treatment of Intrinsic Asthma, Frieda Haumann and Jean Crump

Treatment of Asthma by Inhalation of Aerosol Aminophyllin, S. J. Prigal

Measurement of Circulating Ragweed Antibodies and Antigen, Correlation With Symptoms, Mary C. Johnson and Harry L. Alexander

Reactions to Antipneumococcal Rabbit Serum III and IV, R. H. Pearsall and Oscar Swineford

Studies in Food Allergy: V. Antigenic Relationship of Fish Family, L. Tuft and George I. Blumstein

Allergenic Interrelationship of Epidermis, Blood Serum, and Skeletal Muscle, F. A. Simon

Guest speaker, Professor E. C. Stakman, University of Minnesota (Subject to be announced)

12:30 P.M. Luncheon

2:00 P.M. Symposium on Antihistaminic and Antianaphylactic Drugs

Introduction, S. M. Feinberg, Chicago

Pyridil-N'-benzyl-N-dimethylethylenediamine-HCl, Carl E. Arbesman

Benadryl-(B-Dimethylaminoethyl Benzhydryl Ether-HCl) experimental and clinical data, Sidney Friedlander

"Benadryl"—Clinical data, George L. Waldbott

"Benadryl"—Clinical data, S. J. Levin

"Benadryl"—Clinical data, L. E. Prickman

"Benadryl"—Clinical data, Charles H. Eyermann

3:30 P.M. President's Address; Report of Subcommittee on Undergraduate Education in Allergy

4:00 P.M. Business Meeting

ANNOUNCEMENT OF CERTIFICATION IN ALLERGY BY THE AMERICAN BOARD OF PEDIATRICS, INC.

The American Board of Pediatrics, Inc., at its last meeting in New York City, took final action establishing certification in allergy as a subspecialty of pediatrics.

Certification in pediatrics by the American Board of Pediatrics, is a prerequisite for such certification in allergy. Those who are already diplomates of the Pediatric Board and who wish to be certified in allergy must make formal application to the Secretary of the American Board of Pediatrics, Dr. C. A. Aldrich, 115½ First Avenue, S. W., Rochester, Minn. Those who are not yet certified in pediatrics and who desire certification in allergy as well should indicate this in their application to the Board of Pediatrics as examination in both subjects may be held at the same time.

The application fee for certification in allergy will be $25, in addition to the application fee for pediatric certification.

An Advisory Committee on Allergy has been appointed to act with the Board of Pediatrics in all matters pertaining to the selection and examination of applicants for subspecialty certification. This Committee is identical with the Advisory Committee on Allergy of the American Board of Internal Medicine. The present members of this Committee are:

Harry L. Alexander, M.D.
Robert A. Cooke, M.D.
Leslie N. Gay, M.D.
Harry L. Huber, M.D.
George Piness, M.D.
Francis M. Rackemann, M.D.

In December of this year, Dr. Oscar M. Schloss will be appointed as the pediatric member of this Committee to take the place of the retiring member.

The Advisory Committee on Allergy has already outlined the requirements for applicants who desire examination in the subspecialty of allergy as follows:

1. Two years, full time, in a satisfactory allergy clinic and its hospital (including training in both allergy and pediatrics), or

2. One year, full time, in the allergy clinic and its hospital, and two additional years of full attendance on such an allergy clinic and its activities, or

3. Five years, full attendance, on such an allergy clinic and its activities, or

4. Special training under qualified preceptors, solely or in combination with aforementioned types of training, and such other training as might be felt adequate to prepare an individual for the practice of allergy.

It is the further opinion of the Committee that clinics for such training should fulfill the following qualifications:

1. They should be in hospitals that have been accepted by the Council on Medical Education and Hospitals and by the American Board of Pediatrics for training and certification in pediatrics and for residencies in pediatrics or medicine.

2. The Director of the Allergy Clinic shall be a diplomate certified in allergy by the American Board of Internal Medicine or American Board of Pediatrics.

When accepted, the diplomate will receive from the American Board of Pediatrics a certificate in allergy and will be listed as a specialist in allergy in the official directory of the Advisory Board for Medical Specialties.

Prospective applicants for certification in the subspecialty of allergy may apply to the Secretary of the American Board of Pediatrics, Dr. C. A. Aldrich, 115½ First Avenue, S. W., Rochester, Minn., any time after Nov. 1, 1945.

DIRECTORY OF THE AMERICAN ACADEMY OF ALLERGY

(Continued)

1930 **Piness, George,** 672 South Westlake Ave., Los Angeles 5, Calif.
b 1891. M.D., U. Maryland 1913; Lt. Col., U. S. Pub. Health Reser. Inact.; Cert. in Intern. Med. 1938 and in Allergy 1940; Sr. Att. Med., Cedars of Lebanon Hosp.; Chief, Allergy Clin., Children's and Good Hope Hosps.; Consult. Allergy Barlow Sanatorium; Lect. Allergy, U. Calif.; Lect. in Allergy, Bishop Johnson Sch. Nursing, Good Samaritan Hosp.; F.A.C.P.; A.M.A.; Soc. Invest. Dermat.

1938 **Pratt, Henry Nickerson,** 66 Laurel Rd., Chestnut Hill, Mass.
b 1902. A.B., Harvard 1924; M.D., 1930; Lt. Col., M.C., A.U.S.; Cert. in Ped. 1936; Asst. Phys. Infants and Children's Hosp., Boston; Vis. Phys. New Eng. Peabody Home for Crippled Children; Instr. Ped., Harvard U.; F.A.A.P.; Royal Soc. Med.; A.M.A.; M., Clin. and Climatol. Soc.; M., Exec. Comm., Soc. Study of Asthma and Allied Cond., 1941-1942.

1937 **Prickman, Louis Elwood,** Mayo Clinic, Rochester, Minn.
b 1897. B.S., U. Pittsburgh 1920; M.D., 1923; M.S.(Med.), U. Minn. 1927; 2nd Lt., Inf., World War I; Cert. in Intern. Med. 1938 and in Allergy 1941; Mayo Clin.; Colonial Hosp.; Asst. Prof. Med., U. Minn., Mayo Fdn.; F.A.C.P.; A.M.A.; M., Alumni Assn. Mayo Fdn., Sec.-Treas.; Central Soc. Clin. Research, Central Clin. Research Club.

1940 **Prince, Homer Edward,** Med. Arts Bldg., Houston 2, Texas.
b 1903. A.B., U. Texas 1926; M.D., 1929; Hermann and Methodist Hosps.; Assoc. Prof. Med. Baylor U.; F.A.C.A.; A.C.P.; A.M.A.; S.-W. Allergy Forum.

1923 **Rakemann, Francis Minot,** 263 Beacon St., Boston 16, Mass.
b 1887. A.B., Harvard U. 1909; M.D., 1912; Cert. in Intern. Med. and in Allergy 1937; Phys. Mass. Gen. Hosp.; Lect. Med., Harvard Med. Sch.; A.M.A.; Assoc. A. Phys.; A. Soc. Clin. Invest.; A. Clin. and Climat Assoc., Sec., 1933-1941; Pres., A. Assoc. Study of Allergy 1925; Pres., Harvard Med. Alumni Assoc., 1930-1931.

1935 **Rappaport, Ben Z.,** 55 E. Washington St., Chicago 2, Ill.
b 1897. Premed., Northwestern U. & Lewis Institute; M.D., U. Ill. 1922; Att. Phys. in Med. Michael Reese Hosp.; Asst. Prof. Med. and Head of Allergy Clin., U. Ill.; Soc. Invest. Dermatol.; Amer. Soc. Psychosomatic Med.

1938 **Ratner, Bret,** 50 E. 78th St., New York 21, N. Y.
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1929 **Rinkel, Herbert John,** 2005 Bryant Bldg., Kansas City 6, Mo.
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1927 **Roche, A. F.,** 50 Farmington Ave., Hartford 5, Conn.

1939 **Rogers, Harry Lincoln,** 269 S. 19th St., Philadelphia 3, Pa.
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1941 **Romanoff, Alfred,** 933 Fifth Ave., New York 21, N. Y.
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1930 **Rowe, Albert H.,** 2940 Summit St., Oakland 11, Calif.
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1935 **Rudolph, Jack A.**, Oliver Gen. Hosp., Augusta, Ga.
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1931 **Schenck, Harry Paul**, 1912 Spruce St., Philadelphia, Pa.
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1942 **Schonwald, Philipp**, 718 Fourth and Pike Bldg., Seattle 1, Wash.
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1932 **Sellers, Erle D.**, Clinic Bldg., Abilene, Texas.
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1938 **Service, William Corr**, 1415 N. Nevada Ave., Colorado Springs, Colo.
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1939 **Shahon, Henry I.**, 1st Serv. Com. Det. U., Vet. Adm., Facility, W. Roxbury 32, Mass.
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1939 **Sheldon, John M.**, University Hosp., Ann Arbor, Mich.
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(To be continued.)

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